Synthesis of substituted hydroxyguanidines and related systems.

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Award date:
1983

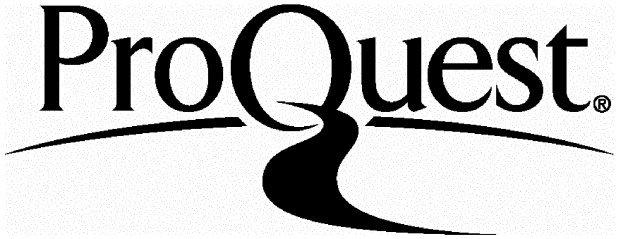
Awarding institution:
University of Bath

TO MY FAMILY AND JACQUELINE

Synthesis of Substituted Hydroxyguanidines and Related Systems.

Submitted by Alastair Peace for the degree of Ph.D of the University of Bath 1983.

Alastair Peace



ACKNOWLEDGEMENTS

The work described in this thesis was carried out in the Organic Chemistry Research Laboratories of Heriot-Watt University, Edinburgh, University of Bath, Bath and Organon Laboratories Limited, Newhouse, Lanarkshire.

I would like to extend my sincere thanks to Professor Malcolm M Campbell and Dr. Alex C. Campbell for their guidance and encouragement throughout this research.

I would like to thank the technicians of Heriot-Watt University and The University of Bath. I would particularly like to thank Miss Sue Green and Mr. Richard Hunter for all their help.

I am very grateful to Professor J.G. Buchanan of Heriot-Watt for his advice in this project.

I would also like to thank all the staff of Organon Laboratories Limited who made my visits there so enjoyable. I would particularly like to thank Mr. John Clark, Mr. Wilson Caulfield, Mr. Maurice Maidment, Mr. John Pick and Miss Joanne Topping for their assistance and friendship. I am also very grateful to Miss Mairi Thomson for the excellent typing of this manuscript.

I would like to acknowledge Dr. D. Williams, Imperial College, London, for supplying X-ray crystallographic data which were invaluable to the research effort and the SERC for a maintainence grant.

Finally I would like to thank my family and Miss Jacqueline Munro for the support and encouragement they have given me.

FOREWORD

Bracketed Arabic numerals in the text refer to the compounds and Arabic superscripts indicate references.

The following abbreviations have been used in the text:-

Ac	acetyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
DMAD	dimethylacetylene dicarboxylate
DMF	dimethylformamide
Et	ethyl
h	hour
HMPA	hexamethylphosphoric amide
HPLC	high performance liquid chromatography
LDA	lithiumdi-isopropylamide
i.r.	infra red
min	minute
mmol	millimole
mol	mol
mp	melting point
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
Nmr	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
RT	room temperature
THF	tetrahydrofuran
tlc	thin layer chromatography
pTSA	p-toluene sulphonic acid

u.v.	ultraviolet
z	benzyloxycarbonyl
Δ	reflux

ABSTRACT

In an extensive study of the annulation chemistry of 2-benzyloxyguanidine, several novel synthetic routes to heterocyclic systems containing the N-hydroxyguanidine moiety were developed.

Two routes to N-hydroxy imidazolines were developed.

1. Reaction of 2-benzyloxyguanidine with chloroacetyl chloride gave 1-chloroacetyl-2-benzyloxyguanidine. Subsequent ring closure to 2-amino-1-benzyloxy-4-oxo-2-imidazoline followed by catalytic hydrogenation gave 2-amino-1-hydroxy-4-oxo-2-imidazoline.

2. Reaction of 2-benzyloxyguanidine with maleic anhydride gave 2-amino-1-benzyloxy-4-oxo-2-imidazoline-5-ethanoic acid. Catalytic hydrogenation then gave 2-amino-1-hydroxy-4-oxo-2-imidazoline-5-ethanoic acid.

A third method involving ring expansion of 2-phenylaziridine-1-carboxamide oxime to give 2-amino-1-hydroxy-5-phenyl-2-imidazoline was also developed.

Reaction of 2-benzyloxyguanidine with methyl propiolate by ester attack followed by internal Michael Addition gave 2-amino-1-benzyloxy-4-pyrimidone. Debenzylation with boron tribromide then gave 2-amino-1-hydroxy-4-pyrimidone hydrobromide.

Finally debenzylation of 1-chloroacetyl-2-benzyloxyguanidine with boron tribromide gave by yet another mode of cyclisation, 3-amino-1,2,4-oxadiazine-5-one dihydrobromide.

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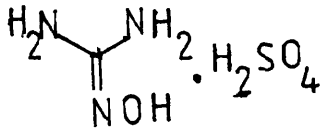
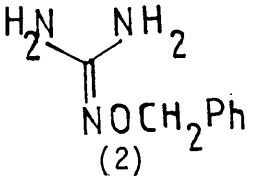
INTRODUCTION

1. General Introduction

Hydroxyguanidine sulphate (1) in addition to its known anti-viral and anti-tumour activity[1] is an immunomodulator[2]. It may reasonably be anticipated that drugs of potential use in the treatment of autoimmune diseases and other disorders of the immune system (e.g. rheumatoid arthritis) may emerge containing the hydroxyguanidine moiety as the effective pharmacaphore. Consequently, the annulation chemistry of 2-benzyloxyguanidine (2) was investigated.



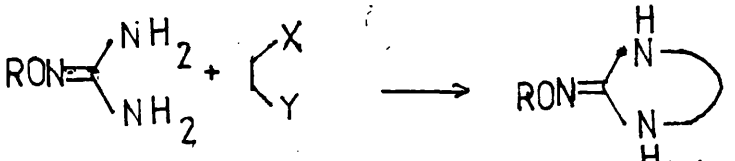
(1)



(2)

Throughout the work, the anticipated modes of cyclisation were:

Scheme 1



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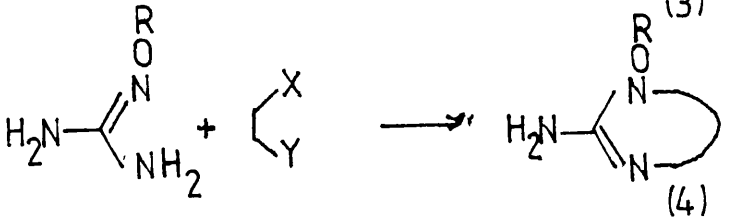

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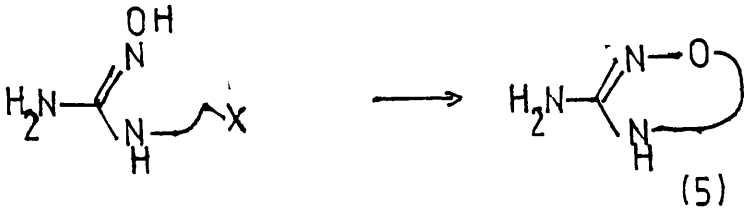

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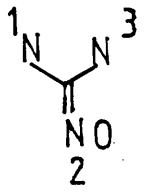
As a result of the likely emergence of structural types (3) and (4) it is pertinent to review their chemistry.

Nomenclature

Hydroxyguanidine nomenclature is as outlined below assigning hydroxyl nitrogen 2.



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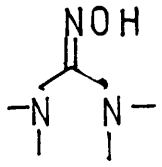
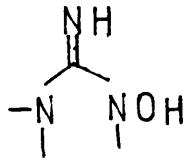


will be referred to as hydroxyimino systems where structure



will be referred to as hydroxyamino systems.

2. Biological Activity of Hydroxyguanidines

2.1 Antiviral and Antitumour Activity

Hydroxyguanidine sulphate (1) was examined for activity against several oncogenic viruses and tumours [1]. The *in vitro* dose of (1) necessary for 50% inhibition (ID_{50}) of Moloney sarcoma virus - Rausher pseudotype M-MSV(RLV) as assayed by reduction in focus forming units, compared with controls, was 2μg/ml. Compound (1) also had cytotoxic effects (inbition of cell growth) against four tumour lines *in vitro*. The ID_{50} as assayed by reduction in cell growth at 24h was 100μg/ml for movikoff hepatroma cells. The dose necessary for 50% inhibition of growth of Walker 256 carcinosarcoma cells in vitro at 48h was also 25μg/ml.

In addition to its antiviral and cytotoxic effects *in vitro*, (1) also had antitumour activity *in vivo* against experimental tumours. (Table 1) Compound (1) produced increases in survival time of 90% and 145% in mice bearing leukaemia L1210 and P388 respectively. Compound (1) was also active in mice bearing the mast cell tumour P815 and rats bearing Walker 256 carcinosarcoma.

Table 1 Activity of Hydroxyguanidine Sulphate (1) Against Various Experimental Tumours

	Range of Doses Tested mg/kg	Optimal Daily Dose mg/kg	% Increase in Median Survival time over that of control
Tumour Mast Cell P815	300-600	500	116
Leukaemia P388	300-600	500	145
Leukaemia L1210	200-800	600	90
Carcinosarcoma W-256	200-500	200	>1000*

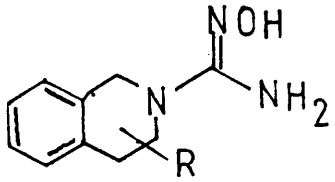
* All rats at this dose level were alive and tumour free more than 5 months after inoculation.

The antiviral activity of the hydroxyguanidinium ion was investigated in the studies of Andreef[3] which showed an effect on cell growth in the S phase, indicating a mechanism of action related to the inhibition of DNA and/or protein synthesis. The exact mechanism of inhibition was not elucidated, but it has been proven to be related mainly to the incorporation of thymidine in the DNA molecule. According to Young[4], the inhibition of thymidine incorporation in DNA takes place through the interference of the hydroxyguanidinium ion with the enzymatic conversions of ribonucleotides to deoxyribonucleotides.

In a molecular orbital study of hydroxyguanidine, Sapse [5] indicated that the hydroxyguanidine ion can dissociate in alkali or neutral medium by loss of hydroxyl proton, leading to the formation of a strong nucleophilic agent which can attack a possible receptor in enzymes, acting in this way as an antitumour and antiviral agent.

2.2 Antihypertensitive Activity - Central Nervous System Activity

Hydroxyguanidines with structure 3,4-dihydro-2-isoquinoline carboxamidoxime (6)[6] exhibited antihypertensitive activity in either of two hypertensitive rat models, (a) renal hypertension produced by latex bag encapsulation of both kidneys[7] (RHR) or (b) the use of the aoki strain of rat[8] (SHR) which has genetically based spontaneous hypertension. The compound was administered orally in 1% tragacanth solution or suspension. The approximate effective dosage (AED) being that dose at which 50% of the animals treated responded with reductions of systolic blood pressure to a normosensitive level (130 nm) averaged around 50 mg/kg.



(6)

6a R = 1 Me
6b R = 1 Me, 3 Me

Fig 1

In the case of (6a) and (6b) activity was recorded at 28 mg/kg and 15 mg/kg respectively. (6a) and (6b) also produced excellent blood pressure control on chronic oral administration to hypersensitive dogs at daily doses as low as 0.3 - 1.25 mg/kg.

Studies were also performed to determine whether (6a) and (6b) would lower blood pressure via a direct central nervous system effect. These studies, in dogs, involved an open chest cross circulation procedure whereby the vascular circulation of the head of one animal was isolated from its systematic circulation, the head being supplied with blood from a donor animal via left arteries and two carotids.

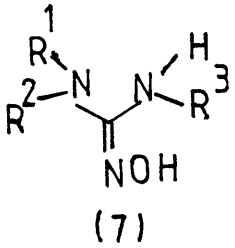
Drug injection was made into the left vertebral vessel. When either (6a) or (6b) was injected in a dose range of 0.4 - 0.8 mg/kg marked (>20%) and sustained reductions in blood pressures occurred

2.3 Antidepressant Activity

Cherkofsky [9] claimed that 1,1,3-trisubstituted hydroxyguanidines (7) could be administered in a pharmaceutical carrier as a treatment for psychiatric depressions of the reactive and endogenous type.

This antidepressant activity was evidenced by tests conducted in female mice in which prevention of tetrabenazine-induced sedation and depression is predictive of human antidepressant response [10]

In the test, relief of ptosis (eyelid closure) was used as the criterion and 1,1,3-trisubstituted hydroxyguanidines (7) prevented tetrabenazine-induced sedation in mice. The ptosis ED_{50} i.e. the dose which blocked ptosis in 50% of the mice is given in table 2.



(7)

Fig 2

	R^1	R^2	R^3
7a	Ph	H	H
7b	H	Me	Me
7c	H	Et	H
7d	Ph	Me	Me

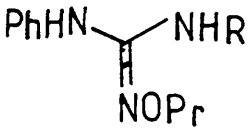
Table 2 Antidepressant Activity of 1,1,3-trisubstituted hydroxyguanidines.

Table 2

Compound	ED_{50} (mg/kg)
7a	<0.3
7b	2.7
7c	<0.3
7d	19

2.4 Antiarrhythmic Activity

Vizas [11] conducted tests on 12 arylhydroxy propanol hydroxyguanidines (8) for antiarrhythmic activity against calcium chloride and barium chloride induced heart arrythmias in rabbits and rats respectively. Eight increased survival and decreased fibrillation.



(8)

Fig 3

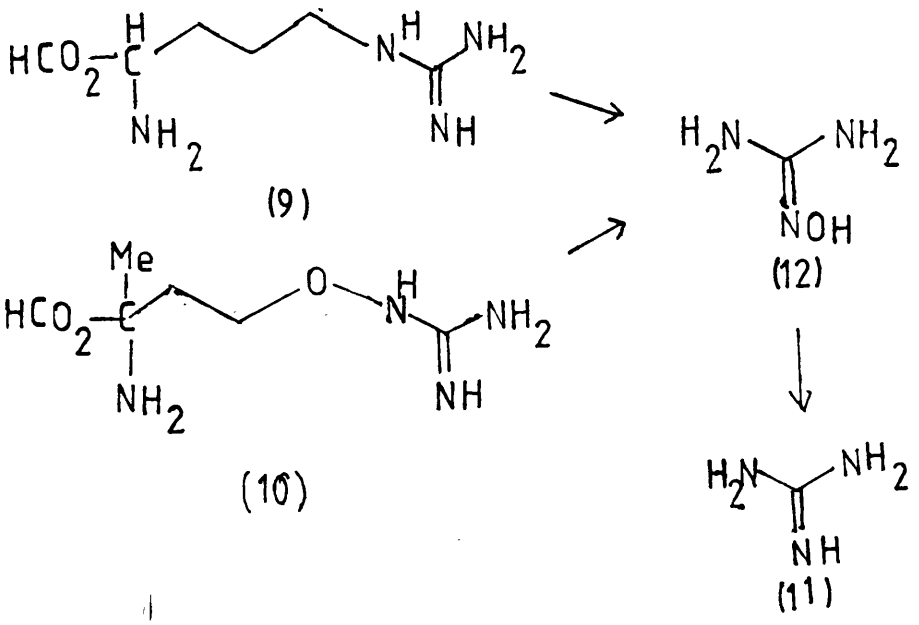
2.5 The Biosynthesis of Hydroxyguanidine In the Mammal

The presence of guanidine in the blood and urine of humans and animals has long been known [12] along with the increased excretion in the urine of patients with chronic renal failure [13]. The parenteral administration of radiolabeled L-canavanine or L-arginine results in the appearance of guanidine in the urine and on the addition of DL-canavanine hydroxyguanidine has been observed [14].

The results of Reiter established that the carbon atom of the guanidine moiety of either L-arginine or L-canavanine is a precursor of the carbon atom of guanidine in the rat.

The biosynthetic pathway is unknown but it was suggested that L-arginine (9) and L-canavanine (10) might be converted directly by either hydrolytic or reductive enzymatic cleavage to yield guanidine (11) or hydroxyguanidine (12) which would subsequently be reduced to guanidine by hydroxyguanidine reductase known to occur in mammalian tissue.

Scheme 2

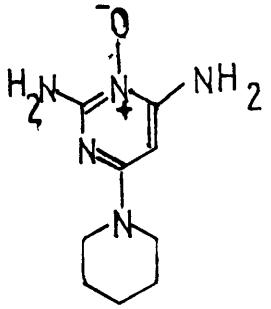


3. Biological Activity of 2,4-Diamino pyrimidine-3-oxides

3.1 Antihypertensitive Activity

2,6-Diamino-4-piperidino pyrimidine-1-oxide (Minoxidil) (13), the parent compound in this series, is a vasodilator with potent antihypertensitive properties[15]. When (13) was administered to nine patients with severe hypertension and renal failure, in daily doses of 10 to 20 mg, satisfactory control of blood pressure resulted in all patients[16]. Supine blood pressure fell from a control valve of 200/124 to 164/91 mg Hg after administration of minidoxil, and no patient experienced orthostatic hypotension.

The exact mechanism of the vasodilator effect of minoxidil is not clear, but it seems probable that vasodilation results from a direct effect on vascular smooth muscle. Hemodynamic studies in animals[15] and man[17] have shown an increase in cardiac output and heart rate after administration of minoxidil. The increase in cardiac output was not due to direct effect on cardiac contractility but, rather, appears to represent a reflex increase in heart rate, contractility, and venous return mediated over the sympathetic nervous system. Total peripheral resistance was consistently reduced after minoxidil therapy.



(13)

Fig 4

4. Chemistry of Hydroxyguanidines (Hydroxyimino Systems)

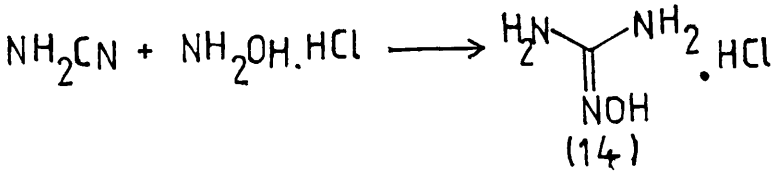
4.1 Synthesis of Hydroxyguanidines

Hydroxyguanidines can be synthesised by the five general routes described below.

4.1.1 From Cyanamides

The first claimed synthesis of hydroxyguanidine hydrochloride (14) over a century ago by Praetorius[18] involved reaction of hydroxylamine hydrochloride with cyanamide. Praetorius experienced great difficulty in isolating the unstable hydroxyguanidine hydrochloride. The reaction products were identified eighty years after as a mixture of ammonium chloride and hydroxyguanidine hydrochloride[19] from which (14) was isolated in 15% yield by ion exchange chromatography.

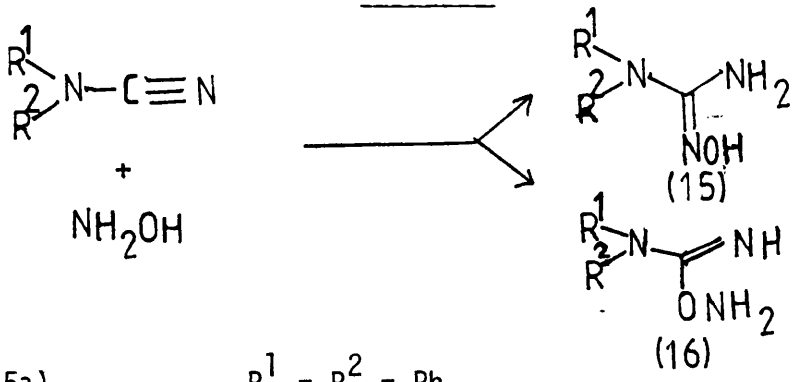
Scheme 3



(14)

Braun and Schuarz[20] claimed the preparation of 1,1-disubstituted hydroxyguanidines by treatment of the disubstituted cyanamide in alcoholic solution with 1 mol of hydroxylamine. The reaction product was more recently shown to be an amino-oxy formamidine (16) by Belzecki's group[21] who found that the addition of hydroxylamine to the nitrile group yielded, depending on the nature of the solvent and substituents at at the nitrogen atom in cyanamide, either 1,1-disubstituted hydroxyguanidines (15) or 1,1-disubstituted-2-amino-oxyformamidines (16).

Scheme 4



(15a) $R^1 = R^2 = Ph$

(15b) (16b) $R^1 = Ph$, $R^2 = Me$

(15c) (16c) R^1 R^2 N- = piperidino

(15d) (16d) R^1 R^2 N- = morphilino

(15e) (16e) $R^1 = R^2 = Me$

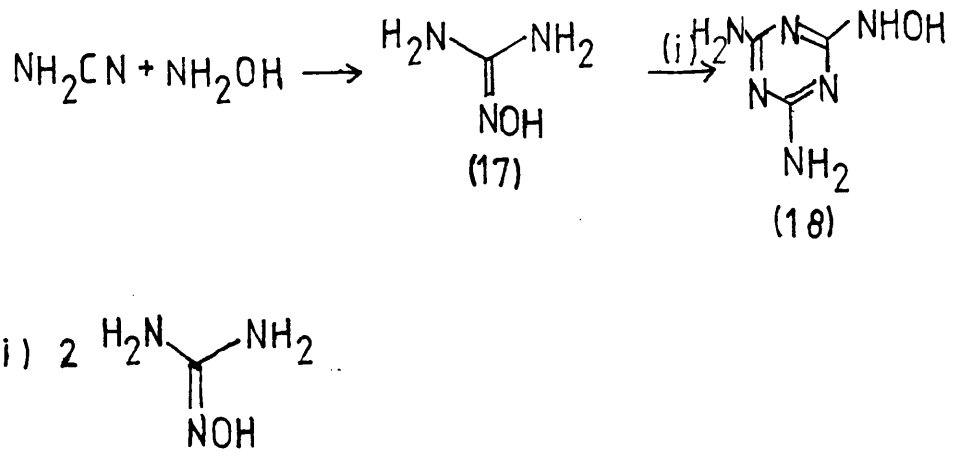
(15f) (16f) $R^1 = R^2 = {}^nBu$

Hydroxyguanidines (15 a - f) which were prepared in yield 50 - 70% when the addition of hydroxylamine was effected in anhydrous dioxan. (15 e and f) Were unstable and could only be isolated as salts.

A similar addition reaction with hydroxylamine in anhydrous ethanol gave (15 a and d) in substantially lower yields whereas the isomeric amino-oxyformamidines (16 b, c, e and f) were obtained instead of the corresponding hydroxyguanidines.

Belzecki[22] claims to have isolated free hydroxyguanidine (17) by reaction of crystalline hydroxylamine with cyanamide. The compound was characterised by ^1H Nmr: a broad exchangeable singlet, reported to intergrate to five protons, possible i.r. bands and a failed CHN analysis. Attempts to purify (17) by recrystallization in warm ethanol resulted, in Belzecki's opinion, in the formation of N-hydroxymelamine (18) again with disputable characterisation

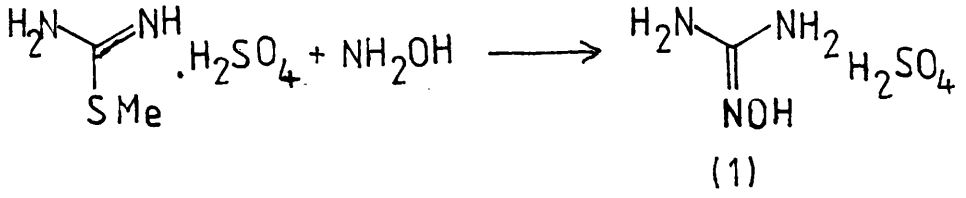
Scheme 5



4.1.2 From Methylthioureas

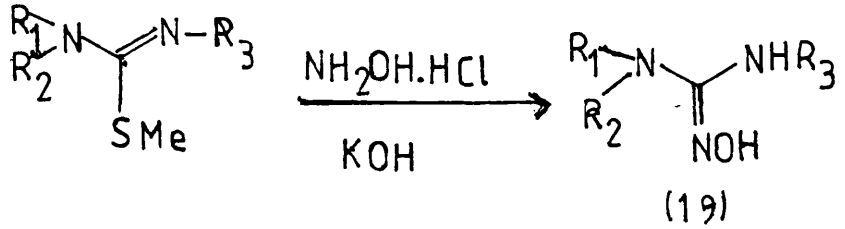
Hydroxyguanidine sulphate (1) can be prepared by the reaction of hydroxylamine with S-methylisothiouronium sulphate [23].

Scheme 6



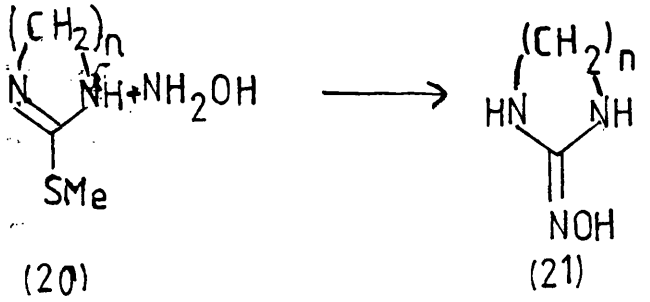
Similarly, substituted hydroxyguanidines may also be obtained by reaction of the isothiourea with hydroxylamine hydrochloride in methanolic potassium hydroxide [9].

Scheme 7



Belzecki[24] claimed to have prepared the cyclic hydroxyguanidines (21) by reaction of hydroxylamine on the corresponding cyclic thioureas (20).

Scheme 8



In our hands the reaction failed and considerable modifications of reaction conditions were required in order to effect reaction.

4.1.3 From Carbodi-imides

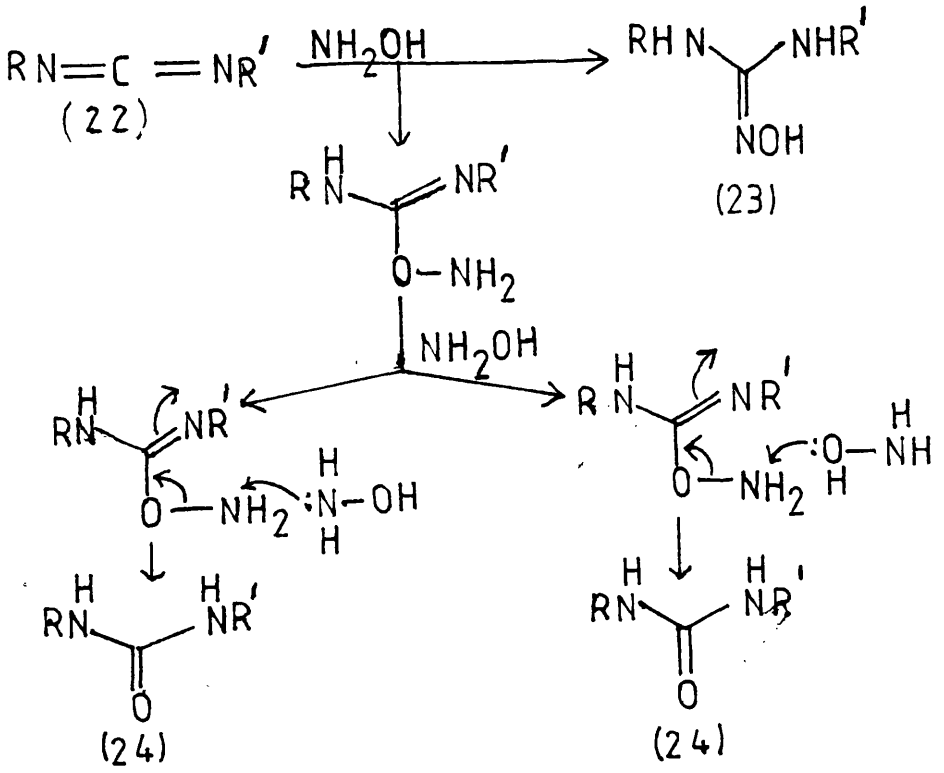
The synthesis of hydroxyguanidines by this route was first attempted by Stolle[25] who reacted hydroxylamine with thiocarbanilide in the presence of lead oxide. In his opinion the product was hydroxyguanidine resulting from the addition of hydroxylamine to carbodi-imide which is formed during the reaction.

Belzecki[26] repeated the reaction several times but could not reproduce the results.

Belzecki further claimed 1,3-disubstituted hydroxyguanidines (1) can be readily obtained by addition of crystalline hydroxylamine to carbodi-imides (22).

Hydroxylamine again reacted as an ambident nucleophile with the reaction products being a mixture of the hydroxyguanidine (23) and analogous urea (24) formed by the suggested mechanism in scheme 9.[26]

Scheme 9

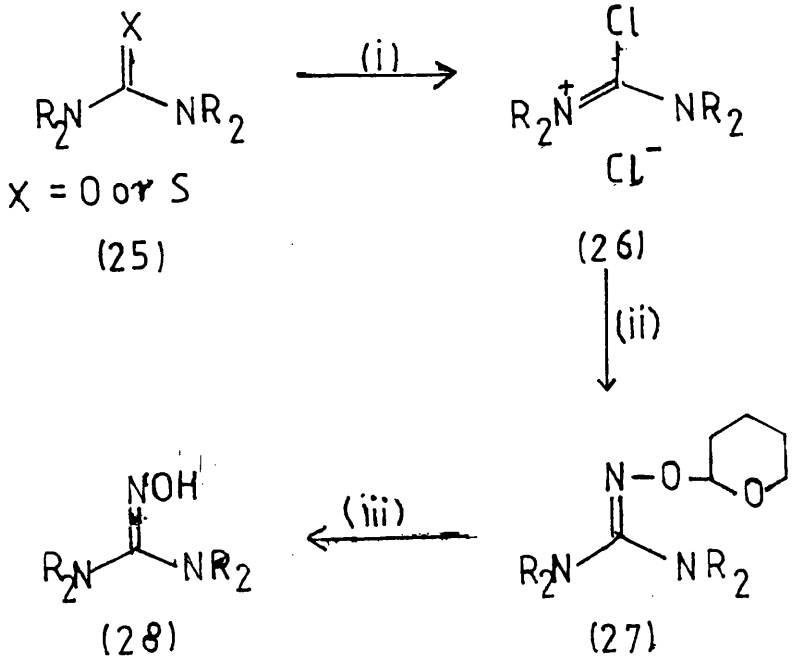


Similarly, by reaction of carbodi-imides with O-substituted hydroxylamines, 1,2,2-trisubstituted hydroxyguanidines may be prepared[27]. As expected electron donating substituents on hydroxylamine facilitated nucleophilic attack by nitrogen and electron withdrawing substituents favoured nucleophilic attack by oxygen.

4.1.4 From C-Chloroformamidinium Chloride Salts

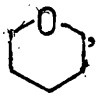
C-Chloroformamidinium chloride salts (26) were prepared by reaction of the appropriate urea (or thiourea) (25) with phosgene [28]. Reaction of (26) with the masked hydroxylamine O-(tetrahydro-2-pyranyl) hydroxylamine and a tertiary amine base gave O-(tetrahydro-2-pyranyl) hydroxyguanidines (27). The yield is high for acyclic compounds and low for cyclics. The protecting group was then cleaved by acid hydrolysis to generate the desired product (28) [29].

Scheme 10



Reagents

(i) $COCl_2$, $PhCH_3$

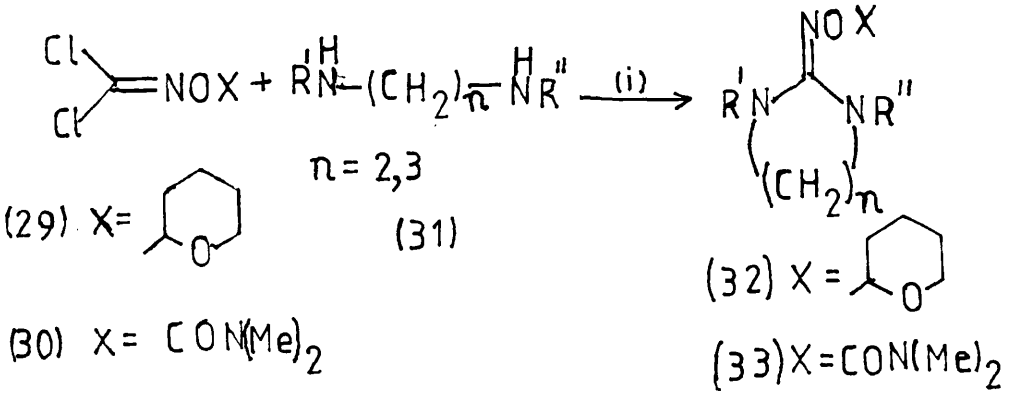
(ii) NH_2-O-  , 2 NEt_3, $CHCl_3$

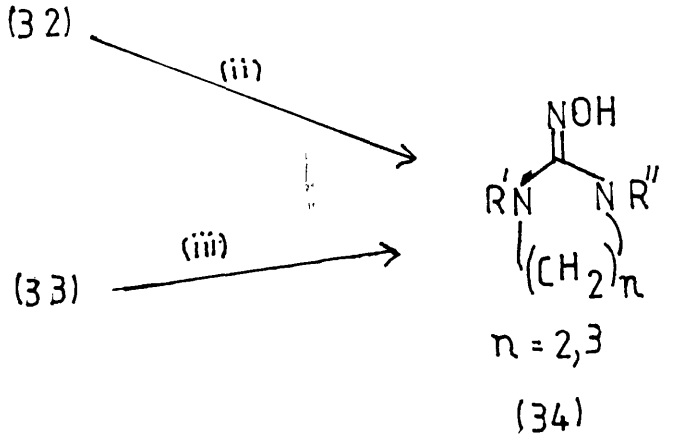
(iii) H_3O^+

4.1.5 From Cyclisation of Phosgene Oxime and Diamine

Cyclictri and tetrasubstituted hydroxyguanidines (34) have been prepared by the reaction of phosgene-O-(tetrahydro-2-pyranyloxime) (29) or phosgene-O-(N-methylcarbamoyl) oxime (30) with a diamine (31) followed by removal of the protecting group by acid or base hydrolysis[29].

Scheme 11





Reagents

(i) $2NEt_3$, $CHCl_3$, reflux

(ii) 3NHCl

(iii) KOH, MeOH

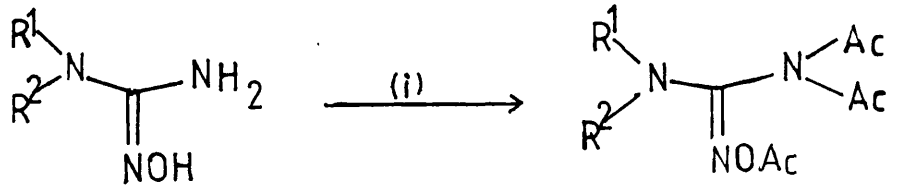
4.2 Reactions of Hydroxyguanidines

The most studied reactions of hydroxyguanidines are acylations as listed below.

4.2.1 Acetylation

1,1-Disubstituted hydroxyguanidines were acetylated with acetic anhydride in pyridine to the triacetyl derivatives (35)[30]. Attempts to isolate any mono or diacetyl derivatives failed, presumably due to their instability.

Scheme 12



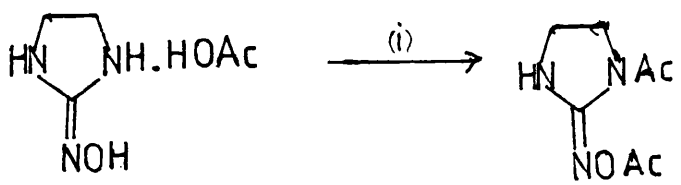
(35)

Reagents

(i) Ac_2O, pyr.

Similarly, the cyclic hydroxyguanidine (12) underwent acetylation to the diacetyl product (36)[10].

Scheme 13



(12) (36)

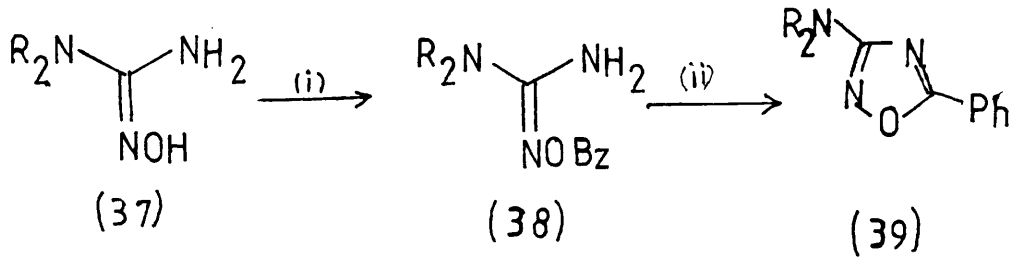
Reagents

(i) Ac_2O, pyridine

4.2.2 Benzoylation

Benzoylation of 1,1-disubstituted hydroxyguanidines (37) led to the monobenzoyl product (38).[30] On prolonged standing the compound cyclised to the 1,2,4-oxadiazole (39).

Scheme 14



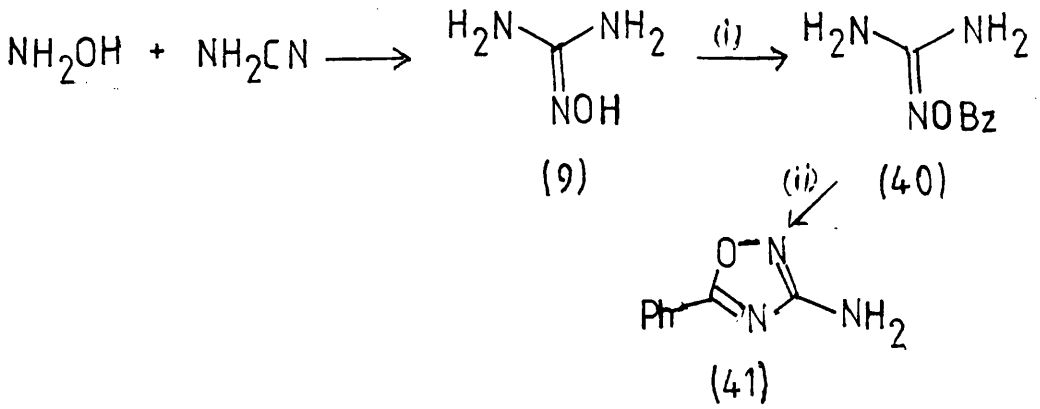
Reagents

(i) BzCl, NaOH, H_2O, immediate

(ii) As above, 1h.

Adams[31] was unable to isolate free hydroxyguanidine (9) and consequently generated (9) in situ from the reaction of hydroxylamine on aqueous cyanamide. (9) was derivatized as the benzoyl product (40) which on rearrangement gave the oxadiazole (41)

Scheme 15



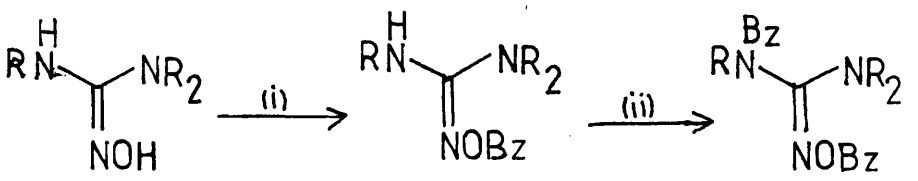
Reagents

(i) BzCl, $NaHCO_3$, H_2O

(ii) NaOH, H_2O

From 1,1,3-trisubstituted hydroxyguanidines (11) Gross [32] isolated monobenzoylated products (42) and the dibenzoylated products (43) unable to cyclise.

Scheme 16



Reagents

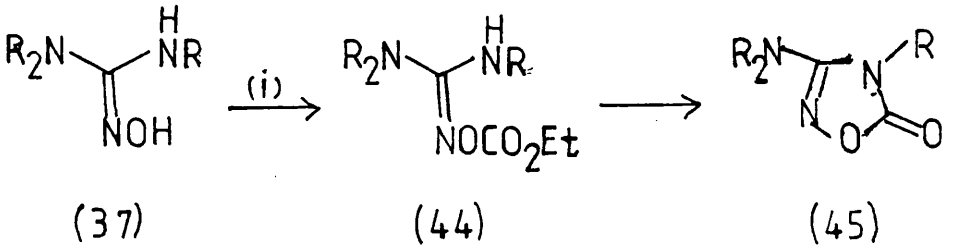
(i) BzCl, pyr

(ii) 2BzCl, pyr

4.2.3 With Ethyl Chloroformate

Belzecki [30] found that 1,1-disubstituted hydroxyguanidines easily underwent O-acetylation with ethyl chloroformate yielding O-ethoxycarbonyl derivatives (44). Where the substituent were methyl, cyclisation to the oxadiazoline (45) occurred. Zinner [33] found that 2-(ethyloxycarbonyl)guanidines (44) cyclised to oxadiazolines (45).

Scheme 17

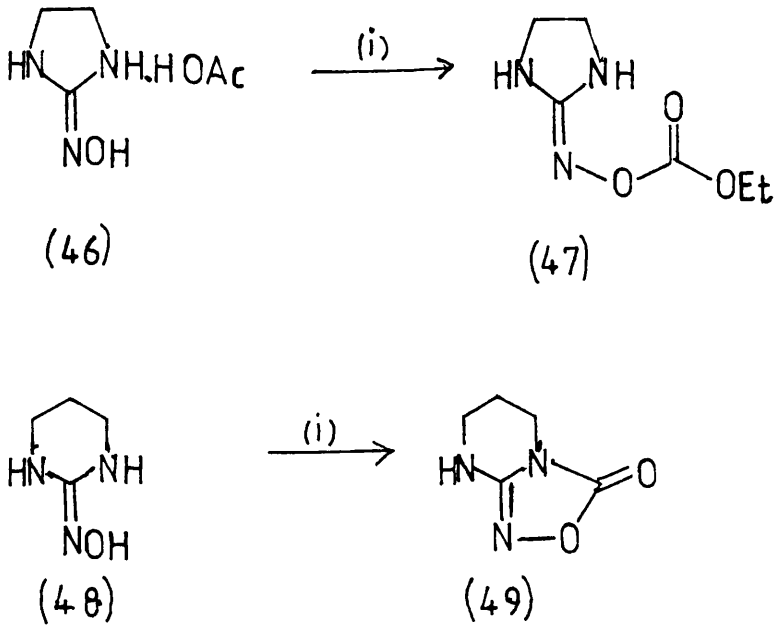


Reagents

(i) $ClCO_2Et$, Na_2CO_3, H_2O

Similarly, with the cyclic hydroxyguanidines, reaction of the 5-membered ring (46) returned the O-ethoxy carbonyl derivative (47) whilst in the 6-membered ring (48) cyclisation to the bicyclic hydroxyguanidine (49) occurred [24].

Scheme 18



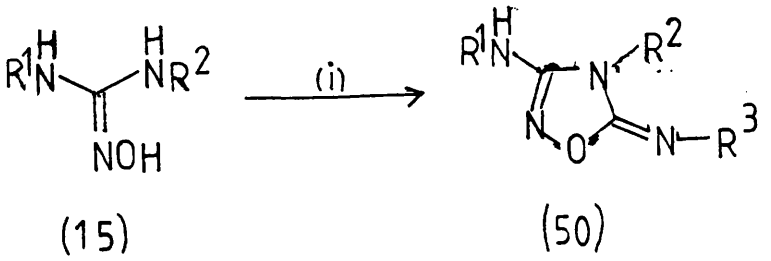
Reagents

(i) $ClCO_2Et$, Na_2CO_3, H_2O.

4.2.4 With Dichloroisocyanates

Zinner [33] has prepared imino-oxadiazolines (50) by reaction of dichloroisocyanates with 1,3-disubstituted hydroxyguanidines (15).

Scheme 19



(15) (50)

Reagents

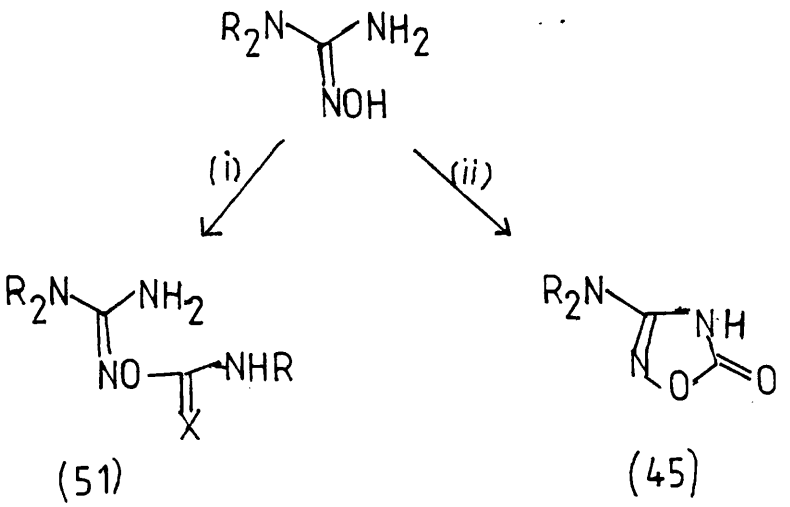
(i) $Cl_2C = N- R^3$, NEt_3, dioxan.

4.2.5 With Isocyanate and Isothiocyanates

Zinner[33] and Belzecki[30] have reacted isothiocyanates and isocyanates respectively with hydroxyguanidines to form the O-acetylated derivatives (51).

In the presence of pyridine Vass[34] effected cyclisation to the oxadiazoline (45).

Scheme 20



(51) (45)

Reagents

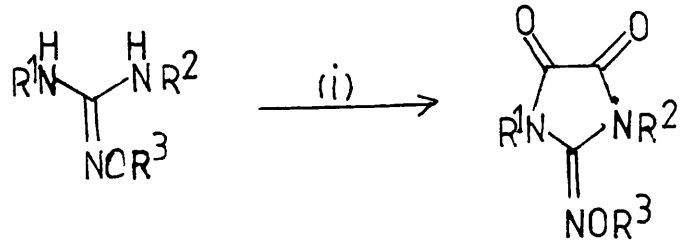
(i) R-N = C = X, X = O or S, MeOH.

(ii) R-N = C = O, pyridine.

4.2.6 With Oxalyl Chloride

1,2,3-Trisubstituted hydroxyguanidines (52) have been reacted with oxalyl chloride to form on cyclisation, 2-imino-4,5-dioxo-imidazolidines (53).

Scheme 21



(52) (53)

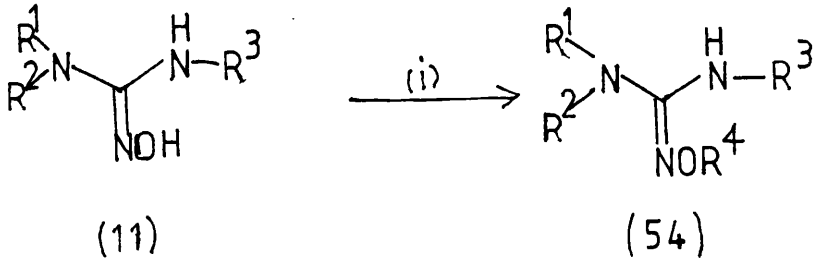
Reagents

(i) $(COCl)_2$, $2NEt_3$, dioxan.

4.2.7 Alkylation with Alkyl Halides

1,1,3-Trisubstituted hydroxyguanidines (11) O-alkylate in the presence of sodium ethoxide[32] to compound of structure (54).

Scheme 22



(11) (54)

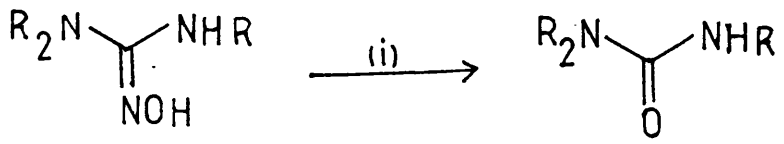
Reagents

(i) R^4-X, NaOEt, EtOH

4.2.8 With Bromine

Gross [32] formed ureas (55) by reaction of bromine on hydroxyguanidines.

Scheme 23



(55)

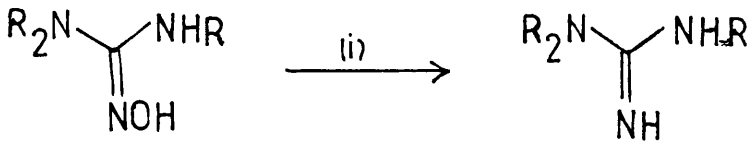
Reagents

(i) Br_2, AcOH.

4.2.9 Hydrogenation

Hydroxyguanidines were hydrogenated to the guanidines (56) under 1 atmosphere hydrogen using Raney-Nickel as catalyst [32].

Scheme 24



(56)

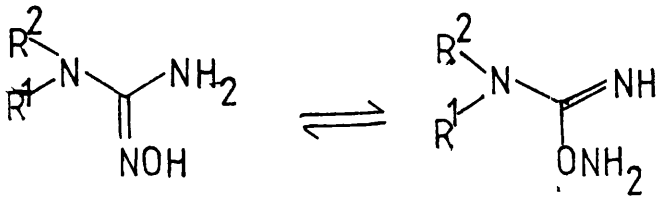
Reagents

(i) Raney-Ni, MeOH, 1 atm H_2.

4.2.10 Reversible Rearrangement:
Hydroxyguanidines Aminooxyformamides

In certain cases, dependent on the substituents, hydroxyguanidines can undergo reversible rearrangement to the aminooxyformamide [21].

Scheme 25



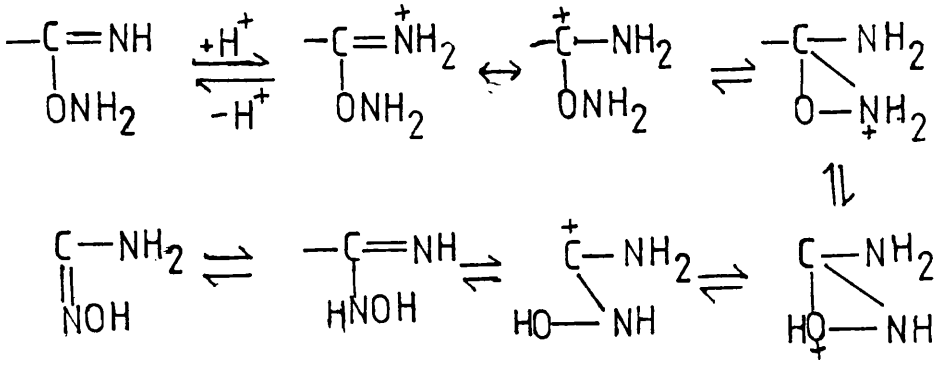
(57) (58)

When (58) (R_1 = Me and R_2 = Ph) is subjected to acidic conditions rearrangement to the corresponding hydroxyguanidine (57) occurs.

An irreversible rearrangement of (57) (R_1 = R_2 = nBu) to (58) occurred when it was stood in ethanol for several days.

The mechanism below has been suggested for the rearrangment.

Scheme 26



The above mechanism accounts well for the rearrangement of the type (57) ⟶ (58) induced by acids.

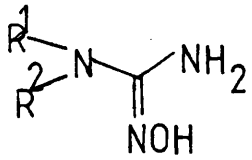
It is suggested that the rearrangement of the type (57) to (58) may be due to a lesser stability of the hydroxyguanidines in ethanolic solutions as compared with their isomeric aminooxy compounds.

Where R R, N = piperidino, reversible rearrangement does not occur

4.3 Spectroscopic Properties

4.3.1 N.M.R.

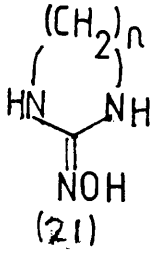
In the case of 1,1-disubstituted hydroxyguanidines (57) confirmation for the oxime structure was found from the proton magnetic resonance spectrum with a sharp resonance at δ8.20 - 8.90 (1H) assigned to oxime proton, which disappeared on deuteration. There was also a broad signal in the range δ4.95 - δ5.60 (2H) from the amine protons [35,36].



(57)

Fig 5

For 1,3-disubstituted hydroxyguanidines (21), where n = 2 the equivalence of the cyclic methylene groups (δ3.3, 4H) could be shown [24]. When n = 3 the presence of a tautomer was indicated by the observation of three exchangeable signals.



(21)

Fig 6

4.3.2 I.r. Properties

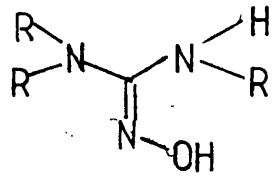
In dilute solutions 1,1-disubstituted hydroxyguanidines (57) exhibit absorption bands at 3610 cm^{-1} (free oxime OH), 3500 and 3400 cm^{-1} (free NH_2) and 1675 - 1640 cm^{-1} (C = N) [21].

Belzecki[27] claimed that free hydroxyguanidine in nitrophenol exhibited absorptions at 3580 cm^{-1} (N-OH), 3510 and 3400 cm^{-1} (NH_2) and in KBr, 1650 cm^{-1} (C = N) [27].

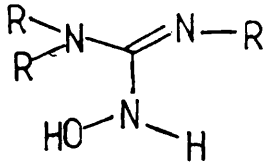
Their spectrum of cyclic hydroxyguanidines (13) exhibited the N-H vibration at 3350 cm^{-1}, the absorption of the associated O-H group at 1680 cm^{-1} and the ν_{N-H} vibration at 1630 cm^{-1} [24]. By comparison with i.r. spectra of derivatives, it was established that the oxime structure existed and that in the investigated system, syn-anti isomers existed.

The spectra of 1,1-dimethyl-3-phenylhydroxyguanidine (59) exhibit bands at 3625 cm^{-1} (free O-H) 3410 (N-H), 3260 (bound OH) and 1650 C = N [37]. The N-O band appeared at 930 cm^{-1} [38].

The above values thus indicated that 1,1,3-trisubstituted hydroxyguanidines existed as urea-oximes (59) and not as hydroxylamine derivatives (60).



(59)



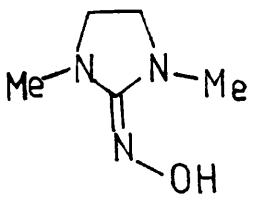
(60)

Fig 7

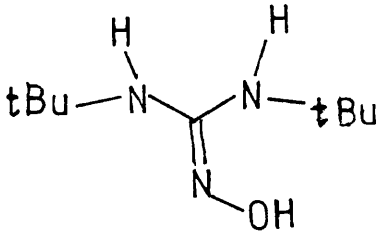
4.4 Physical Properties

4.4.1 Geometrical Isomerisation

The nmr spectrum of (61) obtained in thoroughly dried and deacidified carbon tetrachloride and benzene showed magnetic non-equivalence of N-methyl groups and a singlet of four methylene protons [39].



(61)



(62)

Fig 8

The meticulous purification of the solvent was necessary as

hydroxyguanidines are very sensitive to traces of protonating substances which catalyse the rotational type isomerism below.

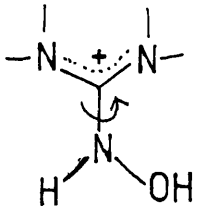
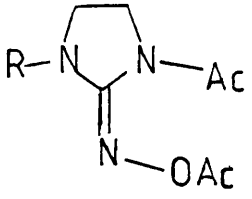


Fig 9

The free activation energy of topomerisation $\Delta G^{\ddagger}$* determined on the basis of nmr spectra of compound (61) with a coalescence temperature T_c = + 57°C, was found to be 67.2 k J mol^{-1}.

The effect of substitution of the ring nitrogen atoms was clearly seen when compound (59) is compared with the acyl derivatives (63 a and b).



63a R = H

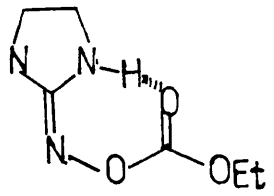
63b R = Me

Fig 10

* According to the nomenclature proposed by Kessler [40] topomers are defined as compounds containing a centre of isomerism but interconverible as a result of isomerisation.

Nmr spectra of these compounds remained unchanged when their solutions in naphthalene were heated to temperatures above 160°. The addition of chloroform has no effect.

It appears that in stable conformations of acetyl derivatives (63 a and b) the acetyl groups are syn. This is indicated by the lack of intramolecular hydrogen-bonding between N-H and carbonyl group (N-H, 3480 cm^{-1}). However, this bonding is present in the O-carbethoxy derivative (64) (N-H 3465 and 3225 cm^{-1}, unchanged by dilution).[39]



(64)

Fig 11

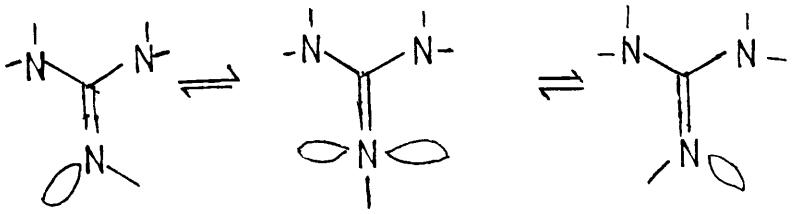
The conformation shown around the N-O bond is unfavourable through synclinical effects of free electron pairs of oxygen and nitrogen atoms, and is only possible through the stabilising effect of this hydrogen-bonding. ($\Delta G^{\ddagger}$ = 79.4 KJ mol^{-1}).

Interestingly, (64) is the only symmetrically substituted cyclic hydroxyguanidine exhibiting non-equivalence of methylene groups. This is presumably due to the formation in benzene solutions, of a complex of benzene with the π-electron system of the guanidine group which is unsymmetrical with respect to the symmetry plane of the imidazoline ring.

The formation of unsymmetrical complexes in benzene has also been observed with 1,3-di-t-butyl-2-hydroxyguanidine (62) where two nine proton singlets appear.

The activation energy of topomerisation of hydroxyguanidines are much lower than those of their O-methyl analogues. This is possibly due to a change in mechanism from inversion to rotation [41].

Inversion



Rotation

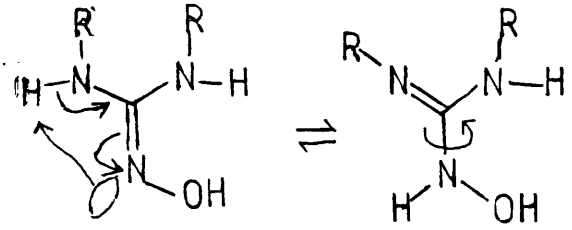


Fig 12

4.4.2 Molecular Bond Lengths and Angles

Hydroxyguanidine molecules and ions were studied in a theoretical self consistent field molecular orbital calculation [3]. The results of the ion with the optimized bonds and angles are given in table 3.

Experimental results obtained by crystallographic studies were given also.

The geometries agreed closely although the theory predicts a slightly larger bond length for the N-O and C-N_1 bonds. The discrepancy was accountable through theoretical calculations not including the negative sulphate ion.

The change in geometry accompanying proton loss from hydroxyguanidine was similar to that observed in guanidine. It resulted in a localisation of the π-electrons on the bond between the carbon and the nitrogen from which the proton was separated, bringing its length to 1.28A$^{\circ}$ followed by a lengthening of the other two bonds.

Table 3

Optimised Bond Lengths and Angles of Hydroxyguanidinium ion

Bond Lengths (A$^{\circ}$)	Experimental Results for 2 ions		Bond Angles	Experimental Angle
C-N1 = 1.34	1.31	1.31	Dihedral H-O	76°
C-N2 = 1.34	1.34	1.33	with the plane	
C-N3 = 1.33	1.33	1.33	of the molecule	
N-O 1.42	1.40	1.39	= 70°	
O-H 0.95	0.96	0.93		

5. Chemistry of Hydroxyguanidines (Hydroxyamino Systems)

5.1 Synthesis of Hydroxyamino Hydroxyguanidines

Few hydroxyamino hydroxyguanidines of the isomeric form (4) are known. The majority are 2,6-diamino pyrimidine-1-oxides.

5.1.1 From Carbodi-imides

It is feasible that the use of N-substituted hydroxylamines in place of O-substituted, should yield non oxime hydroxyguanidines of structure type (65). This method has however only been used in the reaction of carbodi-imides with N-substituted hydroxylamines [34].

Scheme 27

$$RN = C = NR^1 + RNHOH.HCl \longrightarrow \underset{\displaystyle R - \overset{\displaystyle |}{N} - OH}{RNH-C = NR} .HCl$$

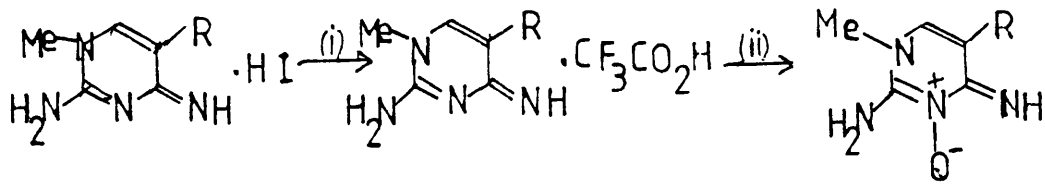
(65)

In all cases substituted carbodi-imides have been used and acyclic compounds with free 1-hydroxy-2-amino guanidine structure type (4) are not known.

5.1.2 By Direct Oxidation of a 2-Amino Pyrimidine

5-substituted-2-amino pyrimidines have been oxidised either as the free bases or trifluoroacetate salts (66) with hydrogen peroxide in trifluoroacetic acid to yield 2-amino pyrimidine -1-oxides (67) [43].

Scheme 28



(66) (67)

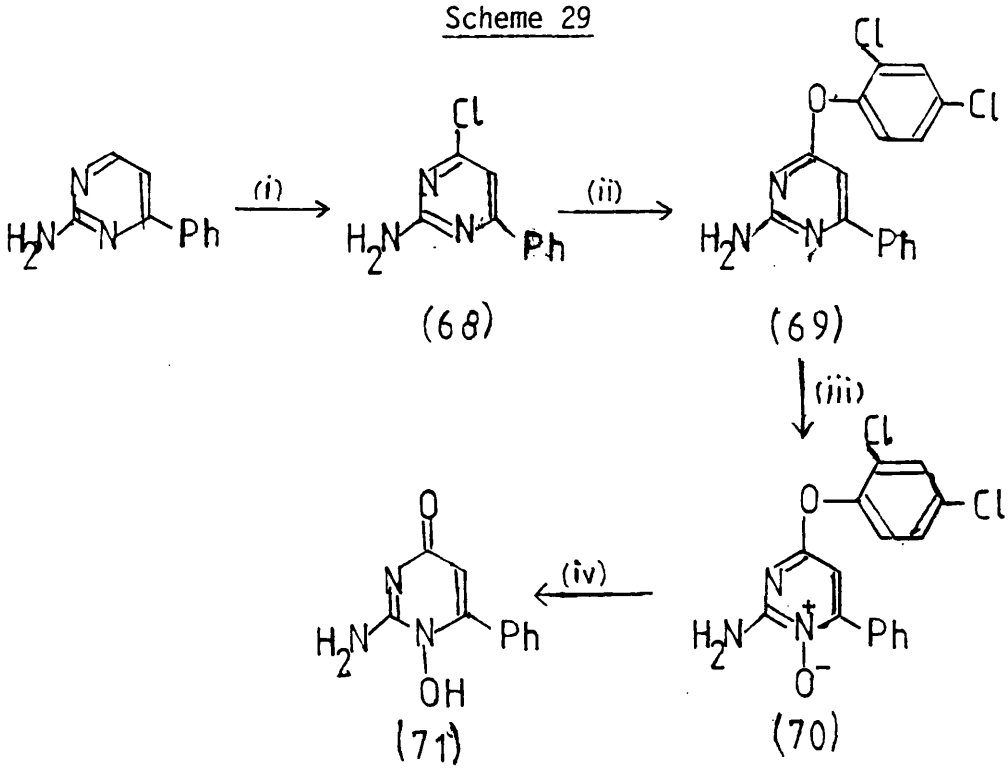
Reagents

(i) Ag CF_3CO_2H, MeOH

(ii) 30% H_2O_2, CF_3O_2H

2-Amino-4-phenoxy pyrimidine (69) obtained from the treatment of 2-amino-4-chloro pyrimidine (68) with 2,4-dichlorophenol yielded on oxidation with mCPBA the 2-amino-4-phenol pyrimidine-1-oxides (70). Subsequent hydrolysis with hydrogen chloride in n-butanol gave 2-amino-1-hydroxy-6-phenyl-4-pyrimidinone (71)[44].

Scheme 29



(68) (69) (70) (71)

Reagents

(i) $POCl_3$

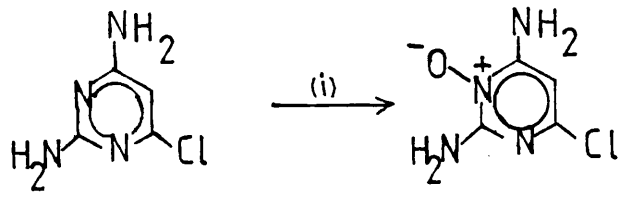
(ii) 2,4-dichlorophenol

(iii) mCPBA, AcOH

(iv) HCl, nBuOH

By oxidation of 6-chloro-2,4-diamino pyrimidine (72) McCall[45] isolated 6-chloro-2,4-diamino pyrimidine-3-oxide (73),

Scheme 30



(72) (73)

Reagents

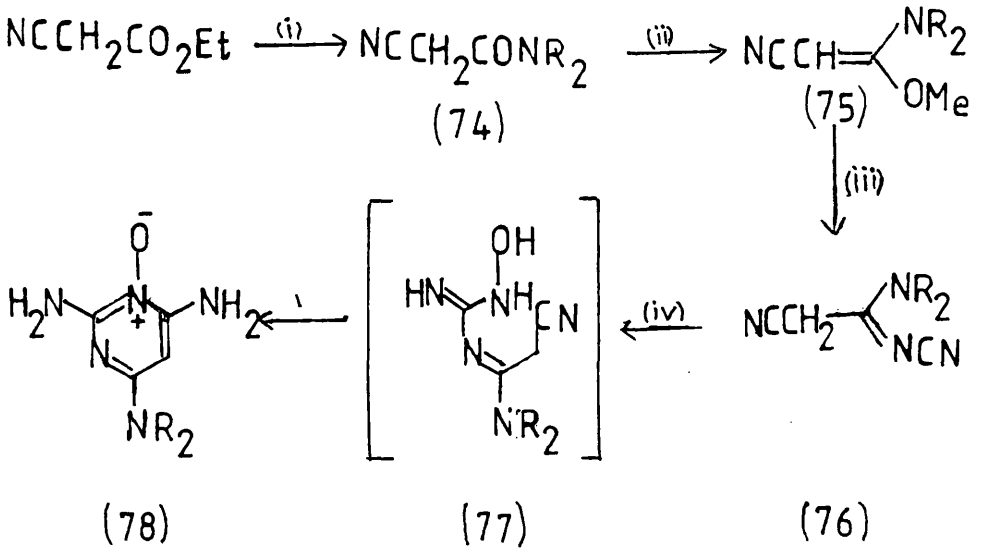
(i) H_2O_2, CF_3O_2H

5.1.3 By Cyclisation

Only one route to the preparation of 2-amino pyrimidine-1-oxides by cylisation has been reported[46]. Reaction of ethyl cyanoacetate with a variety of amines produced the corresponding cyanoacetamides (74) which were O-methylated with either methyl fluorosulphonate or trimethyloxanium flouroborate. Treatment of the resultant salt with either potassium carbonate or sodium methoxide gave the enol ether (75).

Reaction of (75) with cyanamide in alcoholic solvent gave cyanoiminopropionitrile (76) isolated only when NR^1R^2 was piperidine. Treatment of (76) with hydroxylamine yielded triaminopyrimidine N-oxide (78) presumed via the postulated intermediate (77). Yields in most cases were around 50% from (74).

Scheme 31



Reagents

(i) HNR_2

(ii) Me_3OBF_4, K_2CO_3

(iii) NH_2CN

(iv) NH_2OH

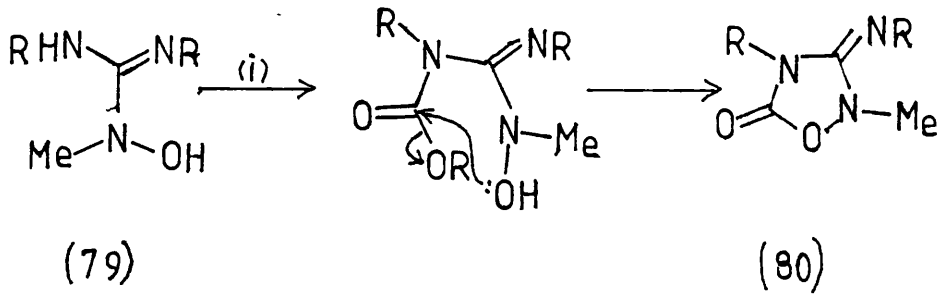
5.2 Reactions of Hydroxyamino Hydroxyguanidines

Many reactions of acyclic hydroxyamino hydroxyguanidines are similar to the hydroxyimino-hydroxyguanidine case.

5.2.1 Alkyloxycarbonylation

Alkyloxycarbonylation of (79) returned the oxadiazolidine (80)[34] by the mechanism indicated below.

Scheme 32



(79) (80)

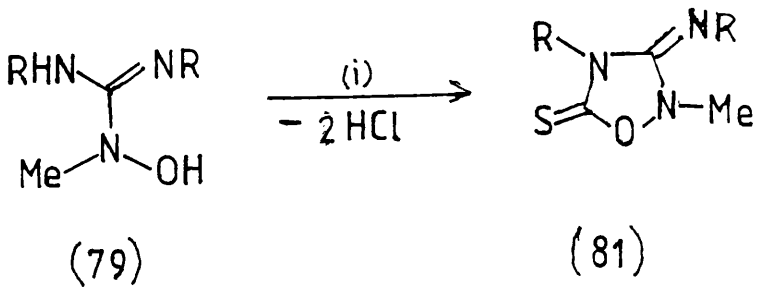
Reagents

(i) $ClCO_2R$

5.2.2 With Thiophosgene

Reaction of Hydroxyamino hydroxyguanidine (79) with thiophosgene produced 2-imino-5-thioxo-1,2,4-oxadiazolidine (81)[34].

Scheme 33



(79) (81)

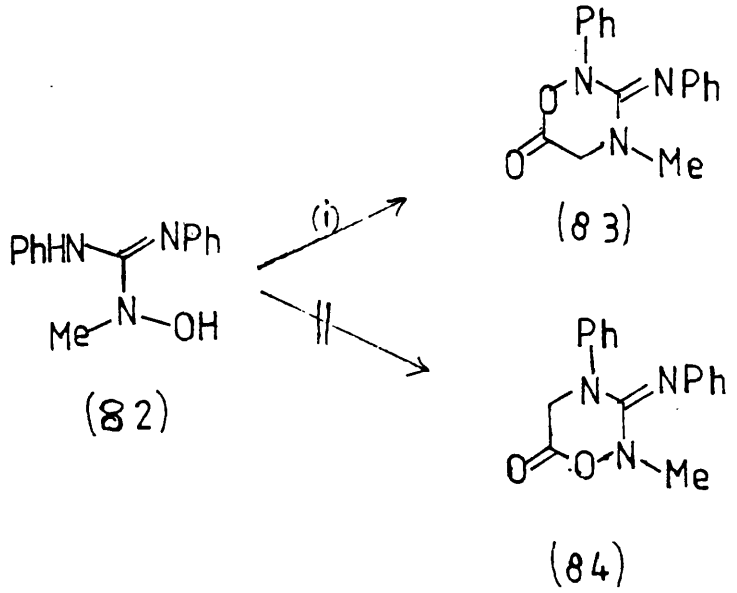
Reagents

(i) $CSCl_2$, $CHCl_3$, H_2O

5.2.3 With Chloroacetylchloride

Voss [34] by reaction of 1,3-diphenyl-2-methyl hydroxyguanidine (82) with chloroacetylchloride in pyridine has obtained the heterocycle (83). The possible formation of structure (84) was eliminated on the basis of mass spectral fragmentation evidence.

Scheme 34



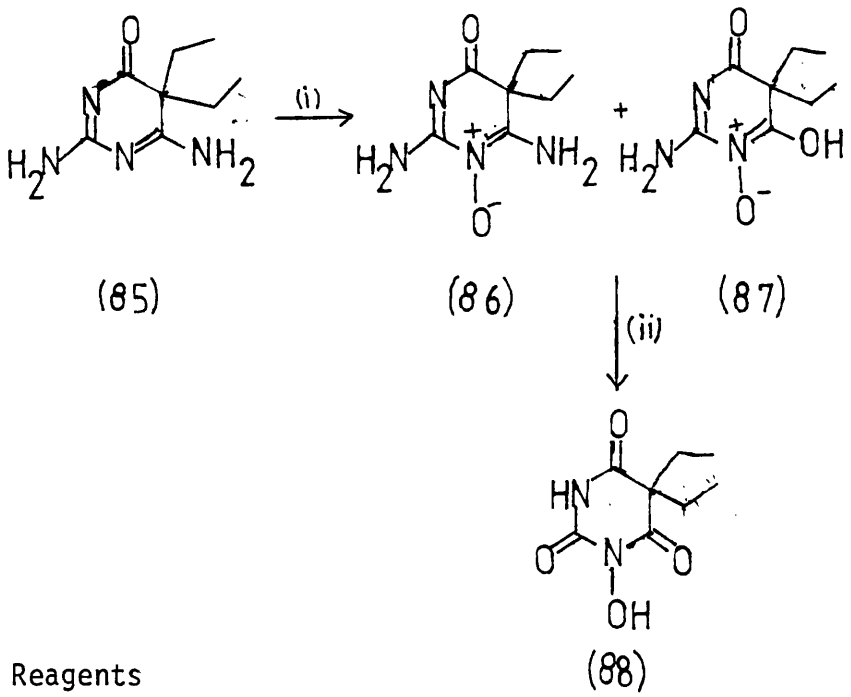
Reagents

(i) $ClCH_2COCl$, pyr

5.2.4 Hydrolysis

Cowden [47] oxidised 2,4-diamino-5,5 diethyl-4-pyrimidinone (85) with m-chloroperbenzoic acid in trifluoroacetic acid in an attempt to form the N-oxides (86) and (87). All attempts to isolate the N-oxides were unsuccessful and consequently the mixture was subjected to acid hydrolysis to give 5,5-diethyl-N-hydroxy barbituric acid (88).

Scheme 35



(85) (86) (87) (88)

Reagents

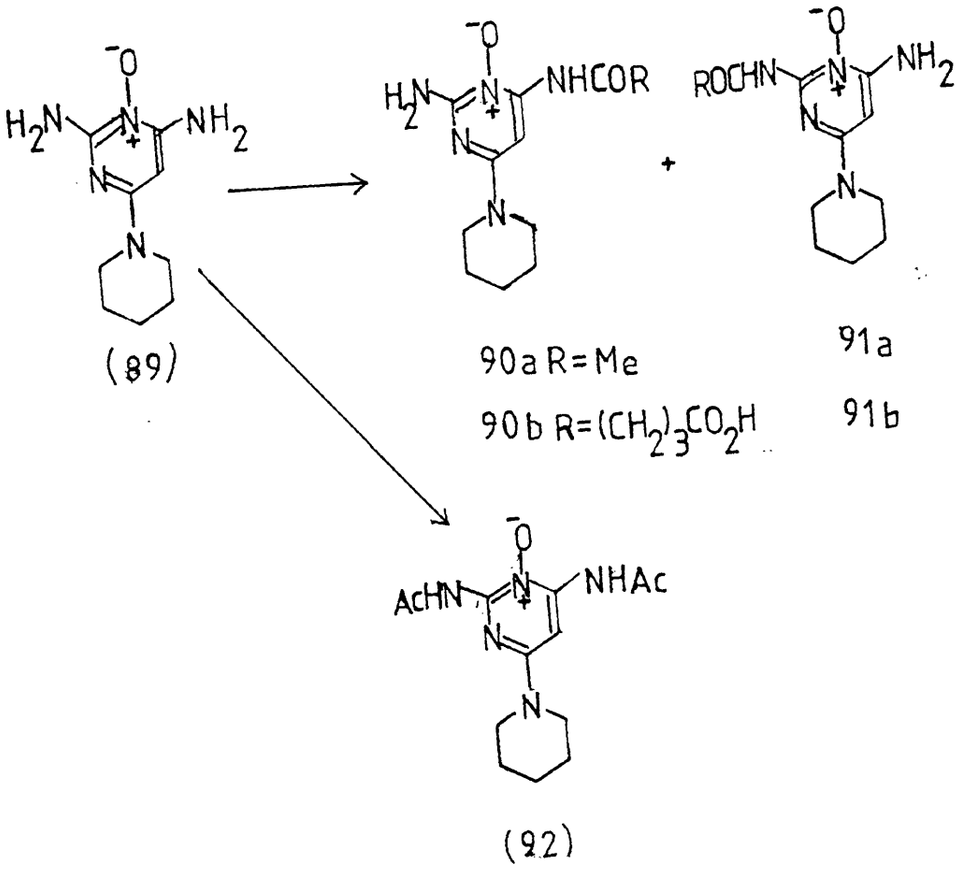
(i) mCPBA, CF_3CO_2H

(ii) H_3O^+

5.2.5 2,4-Diamino pyrimidine-3-oxides and Acid Anhydrides

Acetic anhydride reacted with an equivalent amount of the 2,4-diamino pyrimidine-3-oxide (89) to give monoacetamides (90a) and (91a)[48] in a ratio of 26:1. When (91a) was dissolved in DMSO it gradually converted to (90a) via N-oxide participation. In excess acetic anhydride the 2,4 diacetamide (92) was formed. Glutaric acid reacted selectively with the 4-amino group of (89) to form a single glutaramide (91b).

Scheme 36



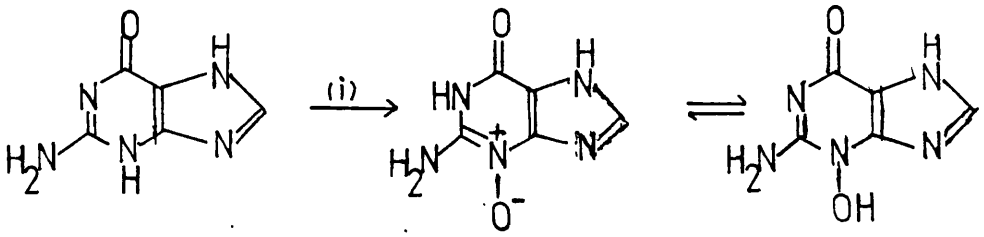
6. Structurally Related Compounds

It is particularly pertinent to review the chemistry and biological activity of 3-hydroxypurines, as our studies centred around monocyclic analogues.

6.1 Synthesis of 3-Hydroxypurines

3-Hydroxypurines (95) are generally synthesized by direct oxidation of the guanine (93) with peroxy acid to give the 3-oxide (94) followed by rearrangement to give the 3-hydroxypurine (95) [49].

Scheme 37



(93) (94) (95)

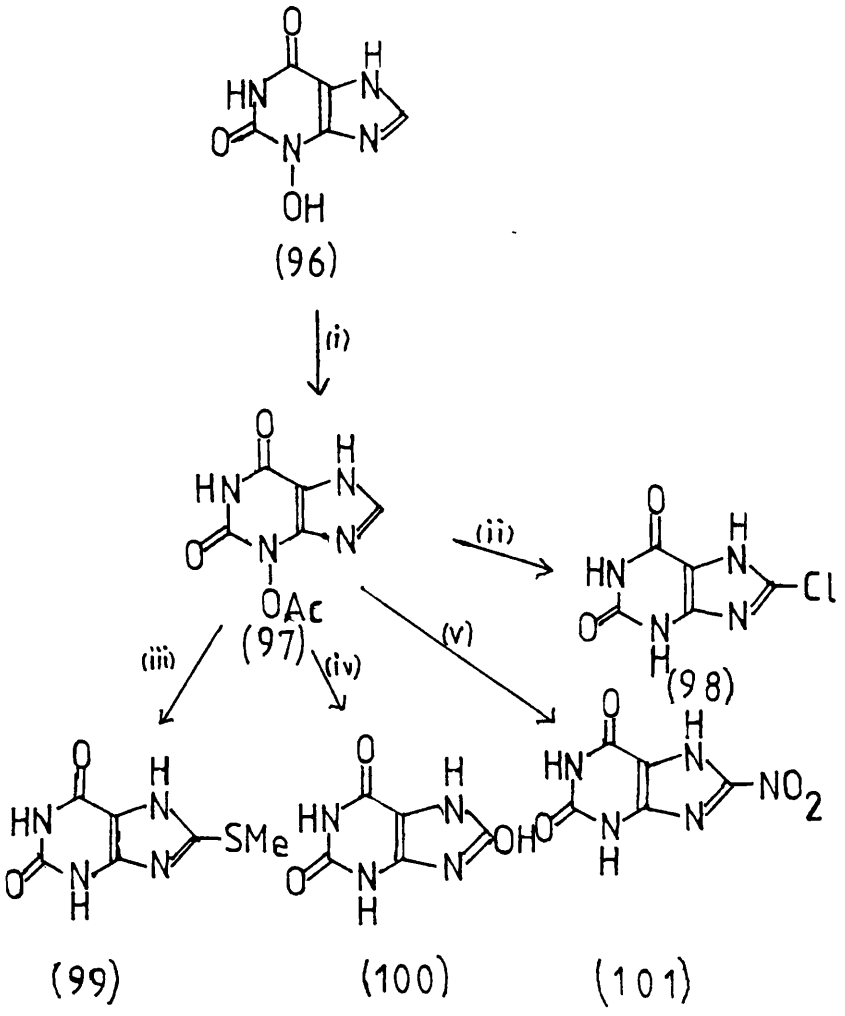
Reagents

(i) H_2O_2, CF_3CO_2H.

6.2 Reactions of 3-Hydroxypurines

3-Hydroxyxanthine (96) and several related N-oxidised purines are stable compounds under many conditions. The 3-acetoxyxanthine (97) derivative is however extremely reactive to nucleophilic displacement [50].

Scheme 38



Reagents

(i) Ac_2O, AcOH.

(ii) NaCl, H_2O.

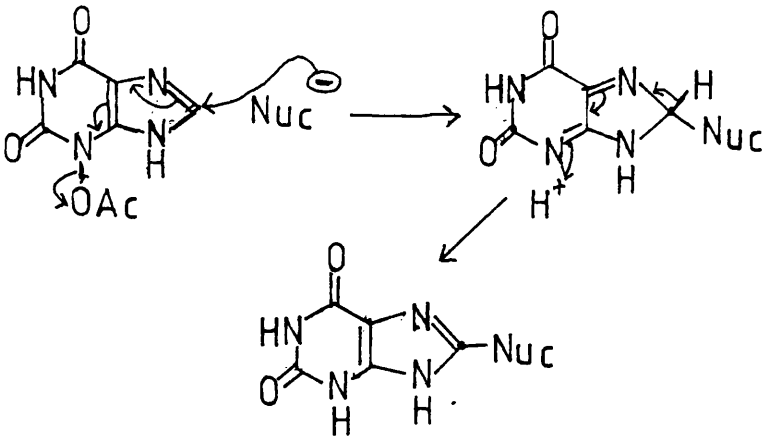
(iii) Methionine, H_2O.

(iv) H_2O.

(v) $NaNO_2$, H_2O.

The following mechanism based on that proposed by Wölcke [51] may occur in the C-8 nucleophilic displacement.

Scheme 39



6.3 Oncogenic Activity

3-Hydroxyxanthine (96) and several related N-oxidized purines are potent carcinogens in rats [52]. Compound (96) induced sarcomas in 88 to 100% of the rats given 24 doses of 1 mg; at 0.1 mg both sarcomas and fibromas appeared in 25 to 58% of the rats. Total doses of 3-hydroxyxanthine ranging from 12 to 66 mg per rat induced S.C. tumours in 25 to 90% of the rats, some of which had hepatocellular carcinomas also.

Two of the urinary metabolites found in the rats were 8-chloroxanthine (98) and 8-methylthioxanthine (99)[53]. The metabolic formation of the 8-substituted chloro-and methylthio-derivatives (98) and (99) is explicable if 3-hydroxyxanthine (96) is converted *in vivo* to an ester with reactivities similar to those of 3-acetoxyxanthine (97). 3-Hydroxyxanthine (96) is thus an oncogen converted *in vivo* to a metabolite having a chemical reactivity which could permit reaction with cell components to initiate the process of chemical oncogenisis.

The oxidative transformation of purines into N-oxide derivatives that are potent oncogenic agents has raised the possibility that such derivatives may play a role in the origin of spontaneous cancers [52].

As will be demonstrated in the discussion section, our studies are highly relevant both synthetically and in terms of potential biological activity, to N-hydroxypurine research.

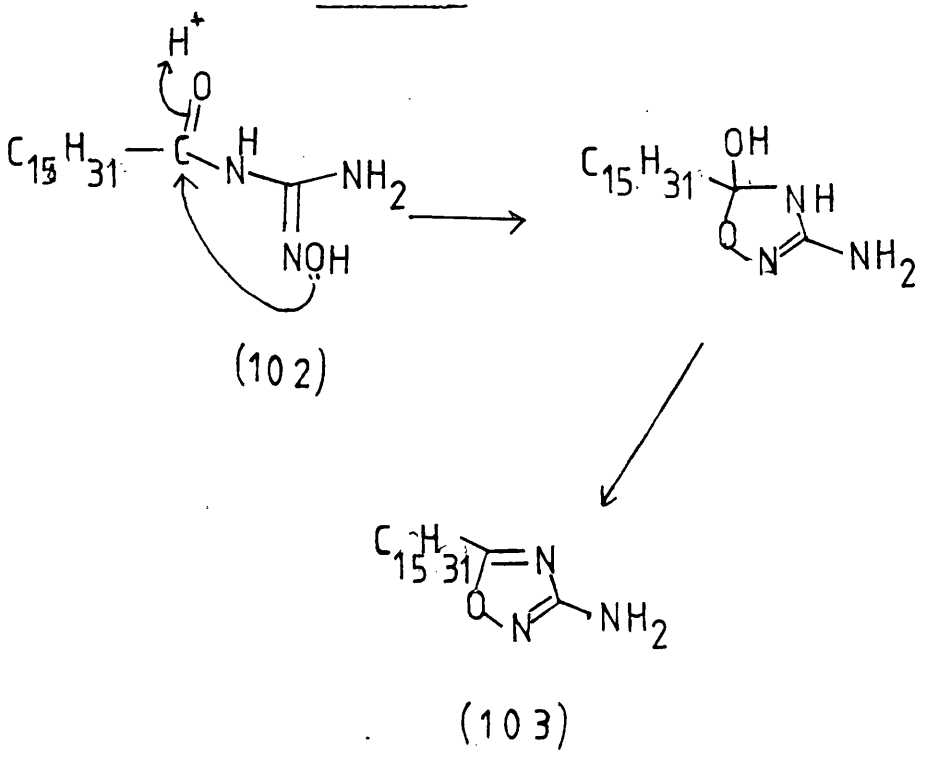
DISCUSSION

7. Displacement of Methanethiol from Cyclic Thioureas with Hydroxylamine

7.1 Synthetic Strategy

As previously mentioned, hydroxyguanidine sulphate (1) is an immunomodulator. However, the compound is too toxic to be of any pharmaceutical use [2]. 1-Palmitoyl-2-hydroxyguanidine (102) is also an immunomodulator [2], although unstable, decomposing in a variety of conditions (e.g. in solution and solid phase) to oxadiazole (103) as indicated in Scheme 40. Decomposition of (102) to the oxadiazole (103) occurred even when (102) was stored in an amber bottle for six months.

Scheme 40

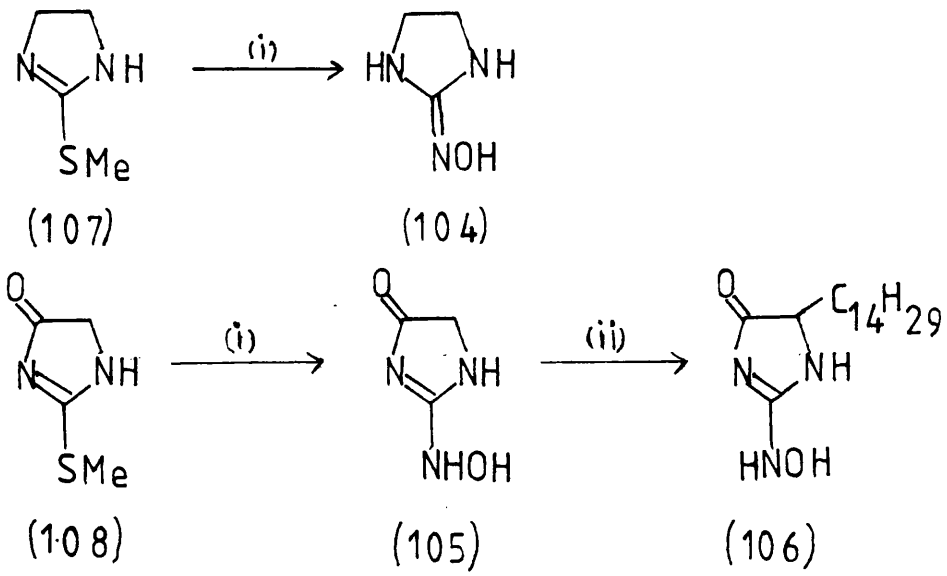


As a result of the above findings, the general objectives in the early phases of this programme were to synthesize exocyclic hydroxyimino heterocycles.

In particular the target compounds were 2-hydroxyimino imidazolidine (104), 2-hydroxyimino-4-oxoimidazoline (105) and 2-hydroxyimino-4-oxo-5-tetradecyl-imidazoline (106). The target compound 2-hydroxy-4-oxo-5-tetradecyl-2-imidazoline (106) has a cyclic structure similar to that of 1-palmitoyl-2-hydroxy-guanidine (102) and may exhibit biological properties similar to (102). Compound (106) would not decompose as did (102) and could reasonably be anticipated to be a more stable compound.

The basic synthetic strategy involved the nucleophilic displacement of methanethiol with hydroxylamine from the cyclic thioureas 2-methylthio-2-imidazoline (107) and 2-methylthio-4-oxo-2-imidazoline (108) to give 2-hydroxyimino-2-imidazoline (104) and 2-hydroxyimino-4-oxo-2-imidazoline (105) respectively. Alkylation of (105) with tetradecylchloride should then give (106).

Scheme 41



Reagents

(i) NH_2OH.

(ii) $C_{14}H_{29}$-Cl, Base.

The problems encountered in pursuit of these synthetic objectives are described in the following sections, together with successful approaches to a range of relevant five-membered ring heterocycles.

7.2 Preparation of 2-Hydroxyimino imidazolidine Acetate (109) and Hydrochloride (110)

In an attempt to prepare 2-hydroxyimino imidazolidine acetate (109) the method of Belzecki et al [24] was employed. This did not give the desired product, presumably due to the presence of mixed salts and the difficulty of judging quantities of the reactive counterparts.

Consequently, 2-methylthio-2-imidazoline (107) was isolated from its hydriodide salt. Several bases were tried, yields being best using ice cold solvents and potassium hydroxide as base (85%). Ammonia liberated (107) in 50% yield, triethylamine gave 14% yield and pyridine gave no reaction.

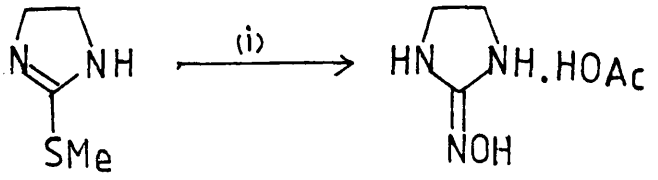
The method of Belzecki was then followed with isolated (107) to return (109) in 30%.

A similar low yield was reported by Belzecki (15% from 2-methylthioimidazoline hydriodide).

To improve the yield of (109) various solvents, molar ratios of crystalline hydroxylamine, times of addition of acetic acid and temperatures were tried. A virtually quantitative yield was obtained using DMF as solvent, addition of acetic acid prior to addition of hydroxylamine and low temperatures (0^{o}).

A molar equivalent of hydroxylamine was necessary as excess addition led to the formation of hydroxylamine acetate.

Scheme 42



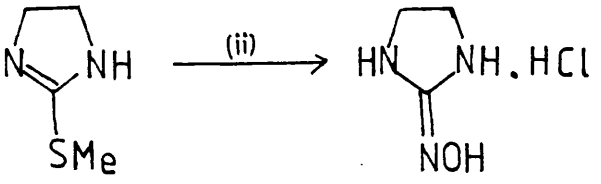
(107) (109)

Reagents

(i) AcOH, NH_2OH, DMF.

Addition of a solution of hydroxylamine hydrochloride in DMF to (107) gave 2-hydroxyiminoimidazolidine hydrochloride (110) in a high yield. (85% from 2-methythioimidazoline hydriodide). This compared favourably to the reported literature best yield of 10% [24].

Scheme 43



(107) (110)

Reagents

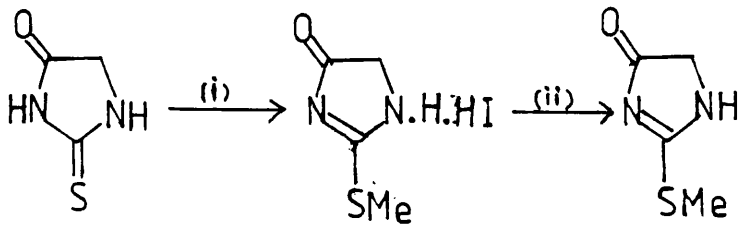
(i) NH_2OH, HCl, DMF.

Attempted synthesis of 2-hydroxyimino-imidazolidine hydriodide (111) by addition of crystalline hydroxylamine to a suspension of 2-methylthio-2-imidazoline hydriodide in dioxan returned starting material. A similar result was obtained using DMF as solvent.

7.3 Attempted Preparations of 2-Hydroxyimino-4-oxo-2-Imidazoline

2-Methylthio-4-oxo-2-imidazoline hydrodide (113) was prepared by methylation of thiohydantoin (112). On a small scale a 2h reflux was sufficient, larger scale reactions requiring overnight periods. 2-Methylthio-4-oxo-2-imidazoline (113) was liberated from its hydriodide salt with potassium hydroxide in 30% yield. Ammonia afforded a 6% yield whilst sodium ethoxide returned an intractable tar.

Scheme 44



(112) (113) (108)

Reagents

(i) 1.1 MeI, MeOH.

(ii) KOH, water 0°.

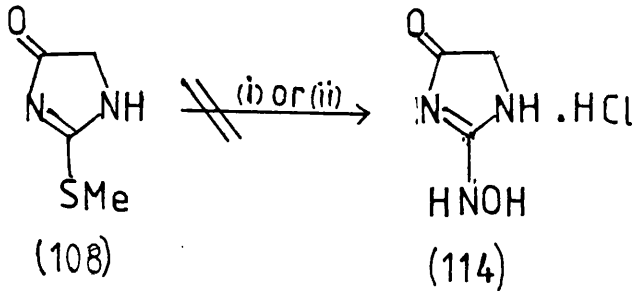
Attempts to displace the methylthio group of (113) or (108) with hydroxylamine to form 2-hydroxyamino-4-oxo-2-imidazoline as the hydrochloride salt (114), the free compound (115), the acetate (116) or the hydriodide salt (117) failed.

The following reactions were tried:

(a) As the hydrochloride salt (114)

Attempted reaction of (108) with hydroxylamine hydrochloride in DMF using conditions developed for (110) gave no reaction. On refluxing the solutions, an intractable mixture resulted. Similarly, using methanol as solvent, starting material was obtained.

Scheme 45



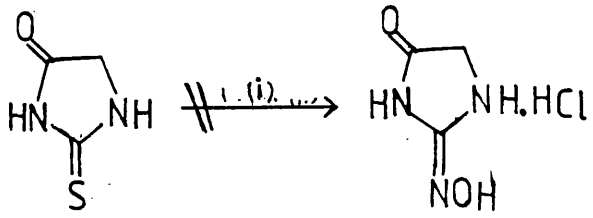
Reagents

(i) NH_2OH, HCl, DMF, RT and Δ.

(ii) NH_2OH, HCl, MeOH, RT and Δ.

An attempt to form (114) by reaction of thiohydantoin (112) with hydroxylamine hydrochloride in refluxing methanol returned starting materials after 7 days.

Scheme 46



(112) (114)

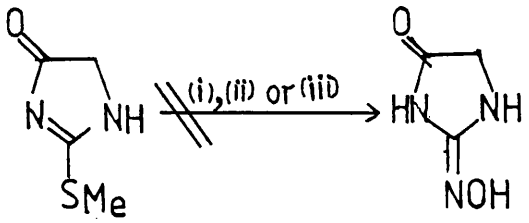
Reagents

(i) NH_2OH, HCl, MeOH, Δ.

(b) As the Free Compound (115)

The addition of a solution of hydroxylamine liberated from its hydrochloride salt with triethylamine in DMF to a solution of (108) returned starting materials at room temperature and an intractable mixture at reflux. Similarly, no reaction occurred on the addition of a solution of the highly reactive crystalline hydroxylamine to a solution of (108) in both DMF and dioxan.

Scheme 47



(108) (115)

Reagents

(i) NH_2OH, HCl, NEt_3, DMF.

Reagents

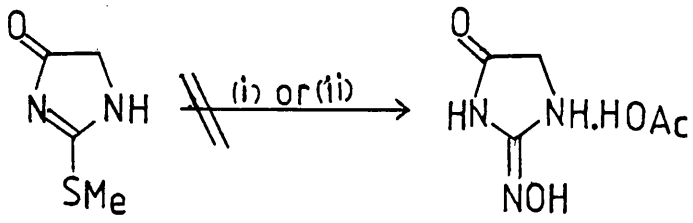
(ii) Crystalline NH_2OH, DMF.

(iii) Crystalline NH_2OH, Dioxan.

(c) As the Acetate (116)

The modified method of Belzecki [24] used to prepare the 2-hydroxyimino imidazolidine acetate (109) was employed, with addition of a solution of hydroxylamine (as either the crystalline compound or liberated in situ with the action of triethylamine on its hydrochloride) to a solution of (108) in DMF. No reaction occurred even after 7 days stirring at room temperature.

Scheme 48



(108) (116)

Reagents

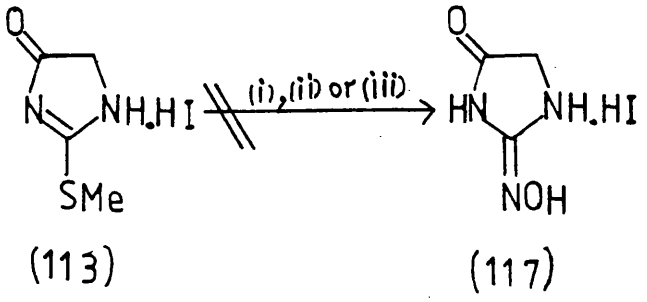
(i) $NH_2OH.HCl$, NEt_3, AcOH, DMF.

(ii) Crystalline NH_2OH, AcOH, DMF.

(d) As the Hydriodide Salt (117)

The addition of a solution of hydroxylamine, liberated from its hydrochloride salt with triethylamine in DMF, to a solution of the hydriodide (113) in DMF gave after 12h an intractable mixture. Conducting the reaction in ethanol, and liberating hydroxylamine in situ from its hydrochloride salt with sodium ethoxide, no reaction was observed. No reaction was observed when crystalline hydroxylamine was added as a solution to a solution of (113) in dioxan.

Scheme 49



(113) (117)

Reagents

(i) $NH_2OH.HCl$, NEt_3, DMF.

(ii) $NH_2OH.HCl$, NaOEt, EtOH.

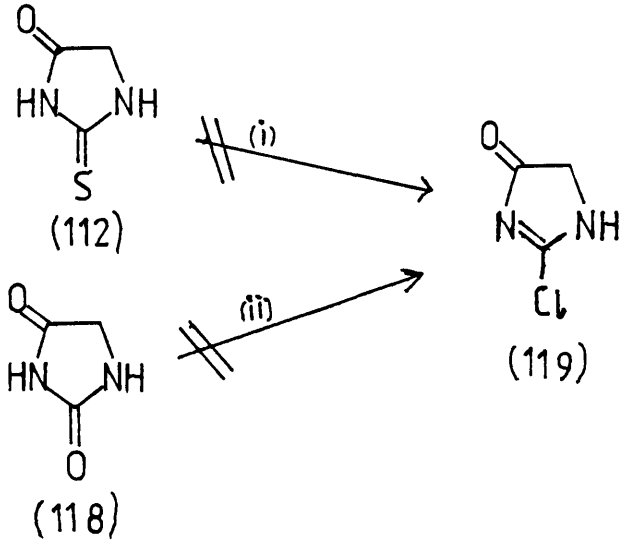
(iii) Crystalline NH_2OH, Dioxan.

Clearly (113) and (108) are very unreactive towards nucleophilic displacement by hydroxylamine.

This unexpected stability of the 2-methylthio-4-oxo-2-imidazoline nucleus may be due to the conjugation between the imine and carbonyl groups which would have to be lost for reaction to occur. Where reaction has occurred i.e. at reflux temperatures, the formation of intractable mixtures may due to the possible instability of the 2-hydroxyimino-4-oxo imidazoline nucleus under the reaction conditions investigated.

Attempts to prepare the possibly more reactive 2-chloro-4-oxo-2-imidazoline (119) by reaction of phosgene on thiohydantoin (112) and by chlorination of hydantion (118) gave intractable mixtures in both cases.

Scheme 50



Reagents

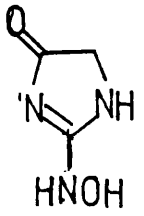
(i) $COCl_2$, pyr, CH_2Cl_2, RT.

(ii) $POCl_3$, Δ.

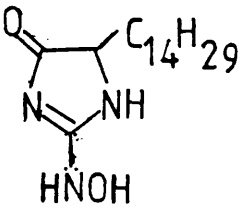
8. Ring Annulation Chemistry of 2-Benzyloxyguanidine and Chloroacetyl Chloride

8.1 Synthetic Strategy

In the light of the unsuccessful studies aimed at the synthesis of compounds numbers (105) and (106)



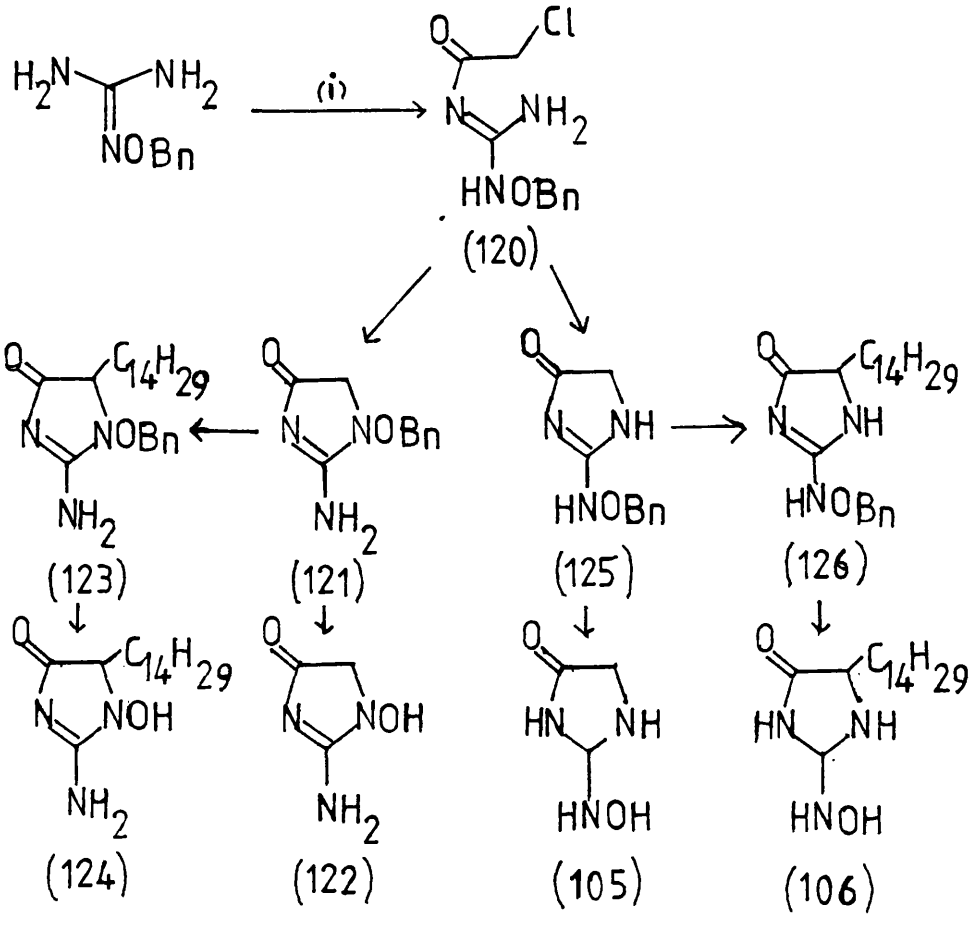
(105)



(106)

a new annulation strategem was devised as outlined in Scheme 51.

Scheme 51



Reagents

(i) $ClCOCH_2Cl$.

It was anticipated that ring closure of 2-benzyloxy-1-chloroacetyl guanidine (120) would give either 2-amino-1-benzyloxy-4-oxo-2-imidazoline (121) or 2-benzyloxyamino-4-oxo-2-imidazoline (125). In either case a new class of heterocycle would be obtained. Alkylation of (121) or (125) with tetradecyl chloride should then give 2-amino-1-benzyloxy-5-tetradecyl-4-oxo-2-imidazoline (123) or benzyloxyamino-4-oxo-2-imidazoline (126) respectively. Debenzylation of (123) or (126) would then give 2-amino-1-hydroxy-5-tetradecyl-4-oxo-2-imidazoline (124) or 2-hydroxyamino-5-tetradecyl-4-oxo-2-imidizoline (106) respectively.

8.2 Synthesis of 2-Amino-1-Hydroxy-4-Oxo-2-Imidazoline

Accordingly, 2-benzyloxyguanidine (2) was prepared by a modification of the procedure of Martin et al[54]. Cyanamide reacted with O-benzylhydroxylamine hydrochloride in refluxing toluene to give 2-benzyloxyguanidine hydrochloride (127). The free 2-benzyloxyguanidine (2) was isolated on addition of 4N sodium hydroxide. As opposed to a 2 hr reflux by Martin, in our hands the reaction required a 48 h reflux in toluene. The hydrochloride salt (127) was not isolated but dissolved as a gum in the minimum of water prior to basification with 4N sodium hydroxide. Yields improved to 85% in contrast to 65% in the literature[54].

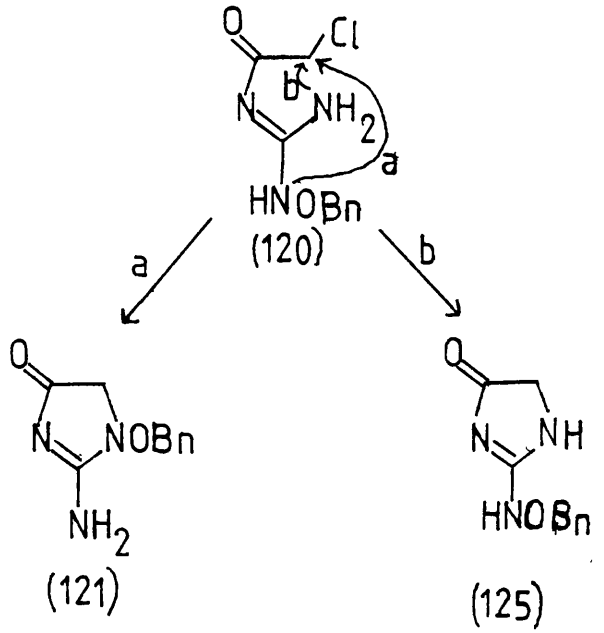
Reaction of (2) with chloroactyl chloride in the presence of triethylamine in THF gave 1-chloroacetyl-2-benzyloxyguanidine (120) in 85% yield. Using pyridine as base, or no base, or ether as a solvent gave (120) in considerably lower yields (<40%).

Similarly, reaction of (2) with dichloroacetyl chloride using identical conditions to the above gave 2-benzyloxy 1-dichloroacetylguanidine (128). Both (120) and (128) exhibited characteristic i.r. absorptions around 3490 and 3380 cm^{-1} ($N-H_2$str), 1690 cm^{-1} (C = O str) and 1670 cm^{-1} (C = N str).

Ring closure of (120) to 2-amino-1-benzyloxy-4-oxo-2-imidazoline (121) was successfully accomplished using one equivalent of sodium hydride in THF. As structure (125) could not be precluded unambiguously via the alternative mode of cyclisation (Scheme 52 route b) by spectroscopic methods, an X-ray structure proof was obtained.

Scheme 52

Alternative modes of cyclisation of 2-benzyloxy-1-chloroacetyl guanidine (120).

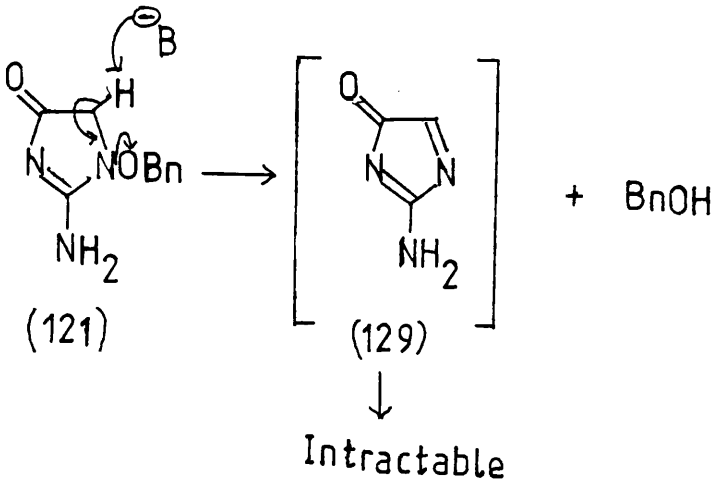


A new class of heterocycle had thus been synthesized. The chemistry was therefore further explored.

Ring closure via $-NHOCH_2Ph$ as opposed to $-NH_2$ may be explained by the alpha effect [55] whereby if adjacent to the attacking atom on the nucleophile there is an atom containing one or more unshared electron pairs, the nucleophilicity is enhanced. Reasons for the effect are not completely understood though it is probably the sum of several factors one being the repulsion between adjacent pairs of electrons.

In the ring closure, yields were good (80%) on the small scale (2.41g, 10 m mol). On scaling up yields diminished dramatically (20%). The reduction in yield was possibly due in part to the competing and faster reaction involving elimination of benzyl alcohol from the product (121) to leave a heterocycle of structure (129) which rapidly decomposed.

Scheme 53

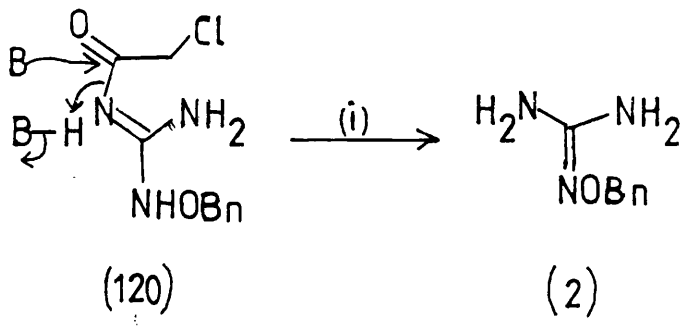


In an attempt to eliminate or reduce this problem encountered on scaling-up, several other bases, solvents and concentrations were tried. Using resublimed potassium-t-butoxide as base a reasonable yield (75%) was obtained with some benzyl alcohol formation.

With triethylamine in THF, no reaction occurred at room temperature and an intractable mixture formed at reflux. Sodium methoxide as base in THF also returned starting materials. Potassium carbonate in acetone gave largely starting material and a complex mixture of products by tlc.

Addition of potassium carbonate to a solution of (120) in methanol unexpectedly gave 2-benzyloxyguanidine (2).

Scheme 54



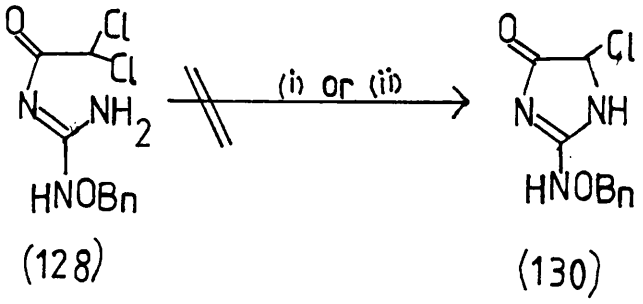
(120) (2)

Reagents

(i) K_2CO_3, MeOH.

Attempts to ring close 2-benzyloxy-1-dichloroacetylguanidine (128) to 2-amino-5-chloro-4-oxo-1-oxybenzyl-2-imidazoline (130) were unsuccessful possibly due to the instability of (130). The use of both resublimed potassium-t-butoxide and sodium hydride as base gave intractable mixtures.

Scheme 55



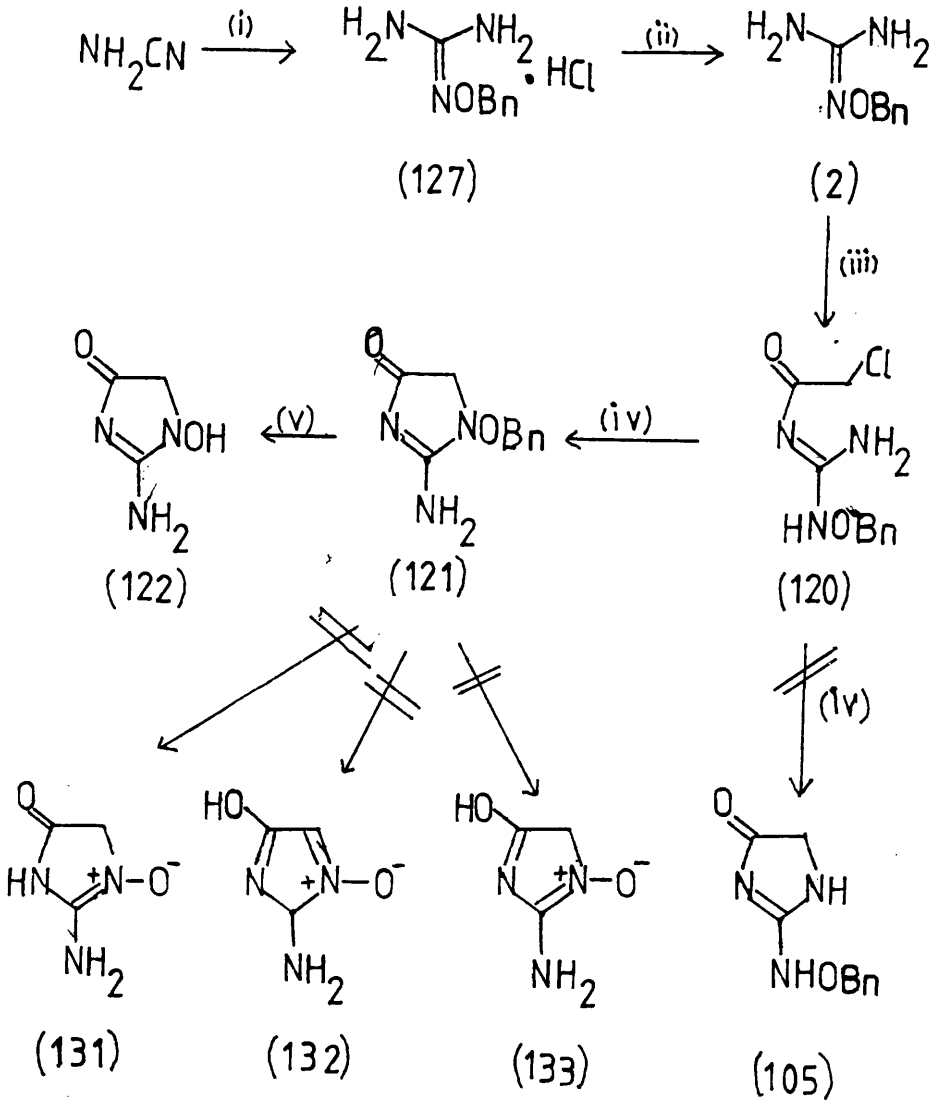
Reagents

(i) Resublimed K O^{t} Bu, THF, RT.

(ii) NaH, THF 0° ⟶ RT.

Debenzylation of (121) was successfully accomplished by catalytic hydrogenation (5% Palladium on charcoal in methanol under 1 atmosphere of hydrogen) to give 2-amino-1-hydroxy-4-oxo-2-imidazoline (122). An attempted debenzylation of (121) with boron tribromide in dichloromethane at -78° gave an inseparable mixture.

Scheme 56



Reagents

(i) NH_2OH,HCl, 48h Δ.

(ii) 4NNaOH, H_2O.

(iii) $ClCH_2COCl$, NEt_3, THF, 0 ⟶ RT.

(iv) NaH, THF 0° ⟶ RT.

(v) 1 atm H_2, 5% Pd/C, MeOH.

The possible formation of N-oxides (131-133) was excluded because the C^{13} C-5 methylene signal and C = O and C = N i.r. stretching frequencies remained unchanged after debenzylation of (121). The presence of an N-oxide was suggested by the appearance of a slight orange-red colouration in aqueous solutions of ferric chloride, characteristic of N-oxides, in contrast to the blue or purple colours produced by hydroxylamine derivatives [47]. Structure (133) is unlikely due to the absence of O-H and presence of C = O absorptions in the i.r. spectrum. It should be realised that ferric chloride may convert one tautomer to the other and give a false result.

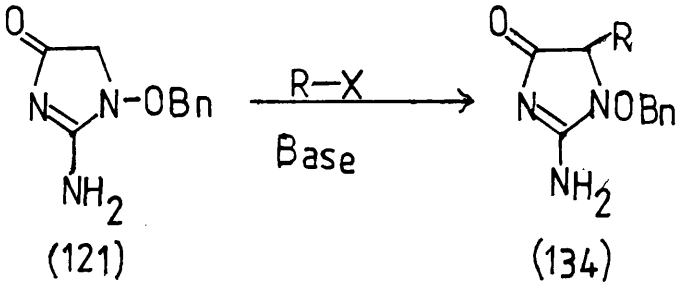
On the balance of spectroscopic evidence, it would appear that (122) would be favoured, although a degree of tautomeric equilibrium may exist.

A new synthetic method for N-hydroxy hydantoins and derivatives has thus been developed. Although two modes of cyclisation from the intermediate 1-benzyloxy-2-chloroacetyl guanidine (120) were theoretically feasible only one was in practice observed.

8.3 Attempted Aklylations of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline

With the aim of adding a lipophilic group to position C-5 of the imidazoline ring in (121) by alkylation, to obtain structure (134), several methylations were attempted on (121) as a model. It was anticipated that N-methylation or simple elimination of benzyl alcohol could occur.

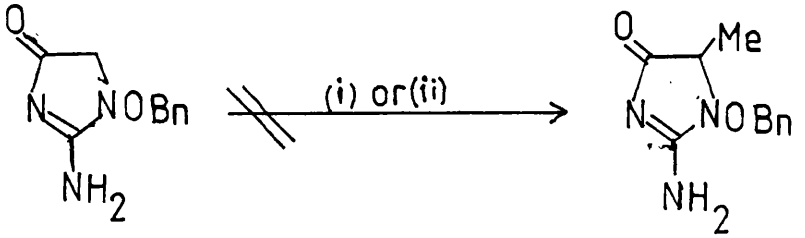
Scheme 57



(121) (134)

Attempted methylations of (121) with methyliodide (1 and 2 equivalents) and LDA (1 and 2 equivalents) in THF and HMPA gave, after aqueous work up, benzyl alcohol as the only isolable product. Extensive extractions of the aqueous layer by addition of salt and n-butanol extraction returned HMPA only. Similarly, using the very strong base dimsyl sodium and methyl iodide in DMSO and aqueous work up, benzyl alcohol was the only isolable product.

Scheme 58



(121) (135)

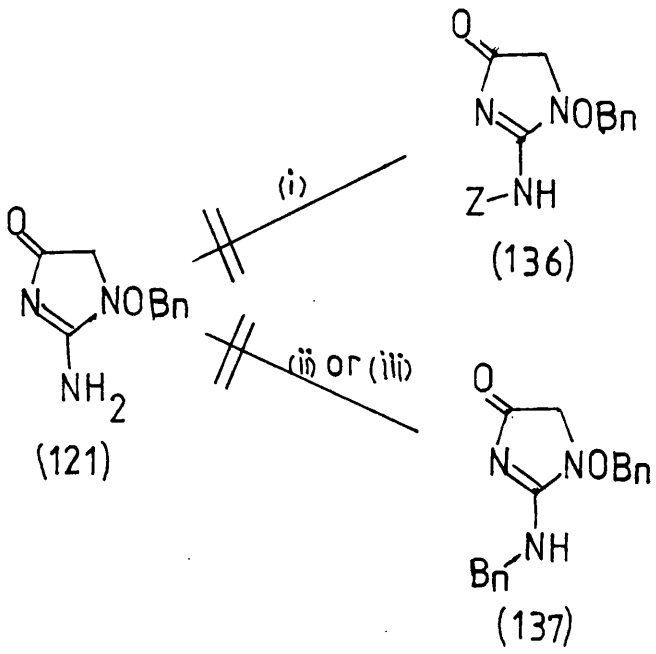
Reagents

(i) MeI, LDA.HMPA, THF.

(ii) NaH, DMSO.

Several attempted N-protections of (121) also failed. By tlc the addition of benzyl chloroformate and potassium carbonate in acetone and water, in an attempt to protect with the benzyl oxy carbonyl (Z) group, resulted in the gradual decomposition of (121) and formation of benzyl alcohol. Attempted N-benzyl protections or C-alkylations with benzyl bromide and potassium carbonate in DMF and benzyl chloride and triethylamine in THF similarly gave intractable products.

Scheme 59



Reagents

(i) $PhCH_2OCOCl$, K_2CO_3, acetone, H_2O.

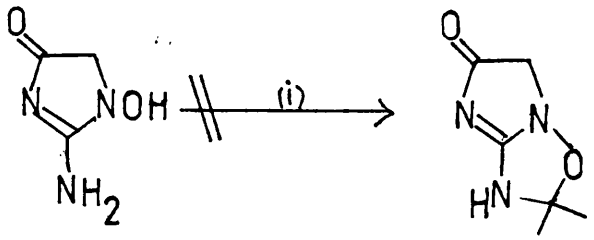
(ii) $PhCH_2Br$, K_2CO_3, DMF.

(iii) $PhCH_2Cl$, NEt_3, THF.

8.4 Attempted Protection of 2-amino-1-hydroxy-4-oxo-2-imidazoline (122)

Finally, an attempt to protect (122) as the isopropylidine derivative (138) failed. A mixture of (122), 2,2-dimethoxypropane and pTSA as catalyst was refluxed for 1h to give an intractable mixture.

Scheme 60



(122) (138)

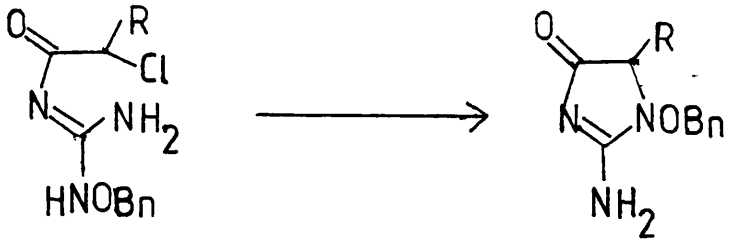
Reagents

(i) $CH_3C(OMe_3)_2CH_3$, pTSA, DMF.

8.5 Preparation of 2-amino-1-hydroxy-4-oxo-5-tetradecyl-2-imidazoline

As a result of several unsuccessful attempts to alkylate (121) at C-5 it was necessary to investigate an alternative strategem, i.e. to introduce the lipophilic group prior to effecting ring closure.

Scheme 61



(139) (134)

α-Chloropalmitoyl chloride (140) was firstly prepared by chlorination of palmitoyl chloride with NCS in thionyl chloride using methods similar to Harpp [56].

Reaction of (140) with 2-benzyloxyguanidine in pyridine and dichloromethane gave 2-benzyloxy-1α-chloropalmitoylguanidine (141) in 34% yield. Several attempts to improve the yield failed. Triethylamine as base and a range of solvents (ether, acetone, dioxan, ethylacetate, THF) were tried. The absence of a base and presence of peroxides led to a disproportionation reaction giving (141) and 2-benzyloxy-1,3-bisdichloropalmitoyl guanidine (142). Short reaction times were also necessary to avoid excessive disproportionation. The product (141) was also unstable to silica and alumina and consequently rapid short path column chromatography through silica was necessary.

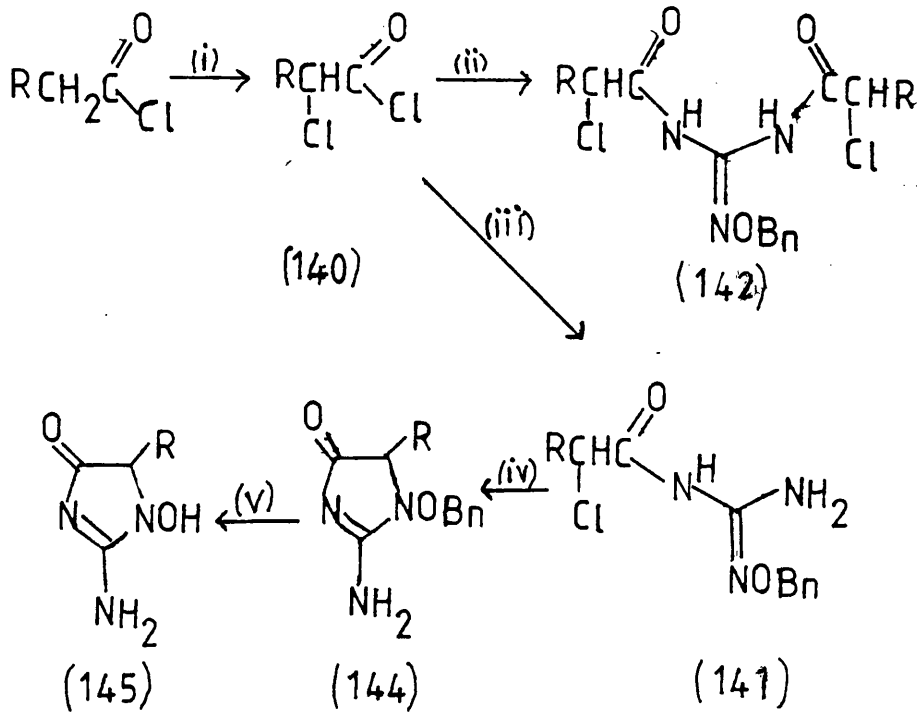
H.P.L.C. grade silica (bondapack C-18 cartridges) was too active returning only small amounts of (141). Disproportionation was a particular problem in peroxide containing ether. Also prepared was 2-benzyloxy-1α-chlorohexanoylguanidine (143).

Ring closure of (141) to 2-amino-1-benzyloxy-4-oxo-5-tetradecyl-2-imidazoline (144) was effected with resublimed potassium-t-butoxide in THF. Earlier, unsuccessful attempts were with sodium hydride (1 mol and excess) at room temperature and reflux, adsorption onto sand and heating at 300°, refluxing in xylene for 24 h, silver tetrafluoroborate, sodium hydride and copper iodide and potassium-t-butoxide. In all cases except for the very severe case with adsorption onto sand and heating at 300° which gave an intractable mixture, starting material was returned in each case.

The difficulty in ring closure is possibly due to steric hindrance from the bulky palmitoyl group. (121) and (144) exhibit the same u.v. absorption thus confirming ring closure of (141) to heterocyclic system (144).

Debenzylation of (144) by atmospheric hydrogenation over 5% palladium on charcoal gave 2-amino-1-hydroxy-4-oxo-5-tetradecyl-2-imidazoline (145). The possible formation of an N-oxide may not be completely excluded, although unlikely due to the presence of an i.r. carbonyl streching frequency at 1660 cm^{-1}. (145) also exhibits an identical u.v. chromophore to (122).

Scheme 62



$R = C_{14}H_{29}$

Reagents

(i) NCS, $SOCl_2$.

(ii) ZCl, peroxide containing ether.

(iii) ZCl, pyr, CH_2Cl_2.

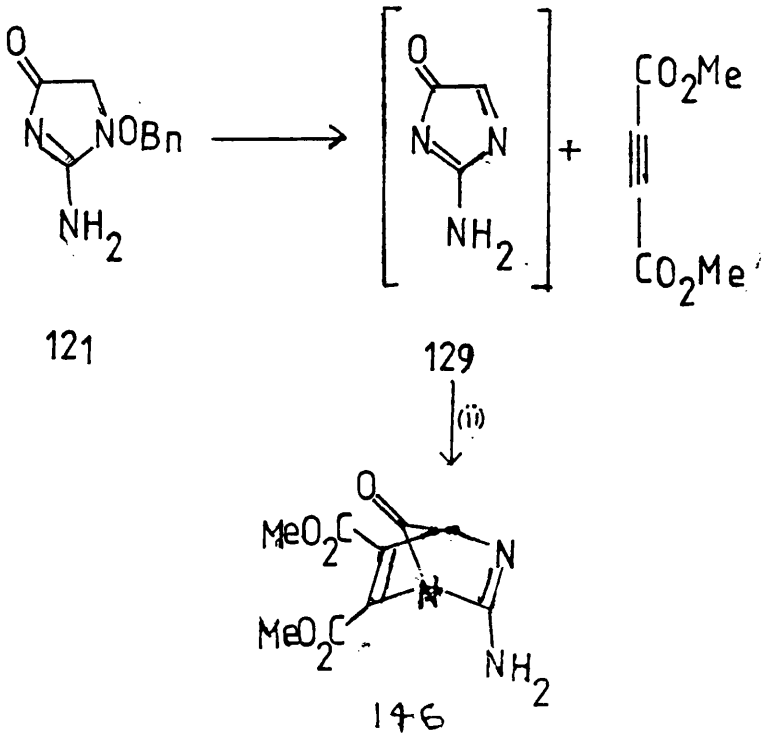
(iv) Resublimed KO ^tBu, THF, 0°.

(v) H_2, 5% Pd/C, MeOH.

8.6 Attempted Trapping of Decomposition Product from 2-amino-1-hydroxy-4-oxo-2-imidazoline

In an attempt to trap the intermediate (129) obtained from elimination of benzyl alcohol with base from (121), sodium hydride was added to a solution of (121) and DMAD. The product (146) obtainable from possible Diels-Alder of (129) with DMAD was not observed and after careful column chromatography on silica benzyl alcohol was the sole isolable product.

Scheme 63



Reagents

(i) NaH, DMF.

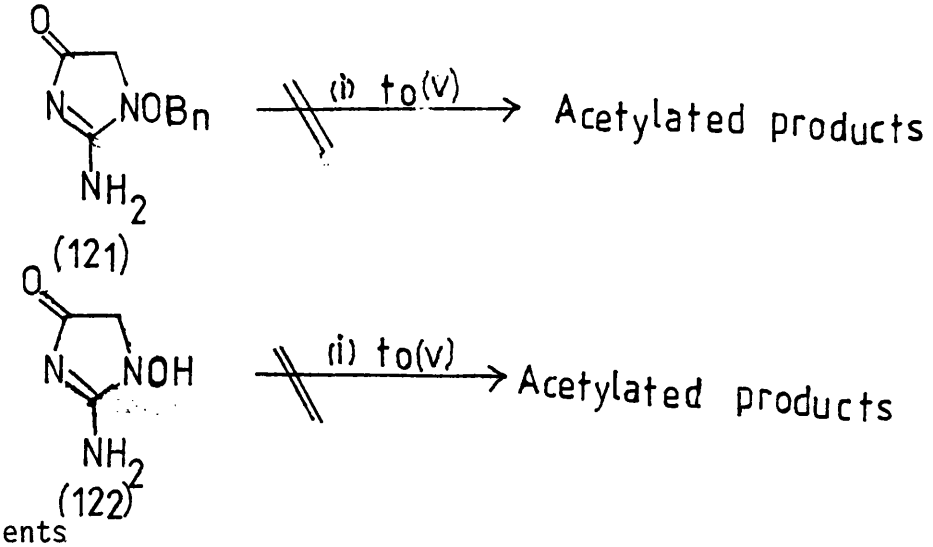
(ii) DMAD.

8.7 Attempted Acetylation, Diazotization and Oxidation of 2-amino-1-benzyloxy-4-oxo-2-imidazoline (121) and 2-amino-1-hydroxy-4-oxo-2-imidazoline (122)

(i) Acetylations

All attempts to acetylate (121) and (122) failed. Using acetic anhydride and pyridine (1 and 2 equivalents and excess) gave in all cases, intractable mixtures. Attempting the reaction in the absence of base gave after column chromatography, benzyl acetate as the sole isolable product.

Scheme 64



Reagents

(i) 1 Ac_2O, pyr.

(ii) $2Ac_2O$, pyr.

(iii) XS Ac_2O, pyr.

(iv) XS Ac_2O, pyr.

(v) Ac_2O, CH_2Cl_2.

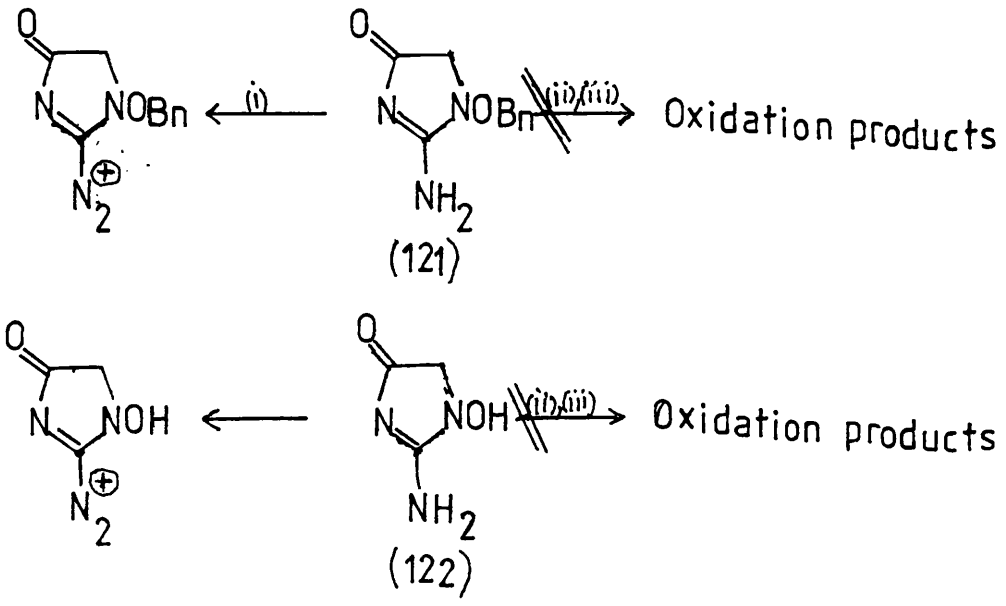
8.7 (ii) Diazotiazation

Attempts to diazotize (121) and (122) with isoamyl nitrite and acetic acid in refluxing toluene gave inseparable mixtures in both cases.

(iii) Oxidation

Attempts to oxidise (121) and (122) were unsuccessful. With mercuric acetate no reaction occurred and with fresh lead tetra-acetate a very polar, inseparable mixture formed.

Scheme 65



Reagents

(i) AcOH, isoamyl nitrite, toluene.

(ii) HgO, THF.

(iii) $Pb(OAc)_4$, THF.

8.8 Reactions of 2-amino-1-benzyloxy-4-oxo-2-imidazoline (121)

Reaction of imidazoline (121) with chloroacetyl chloride in refluxing THF gave the intermediate (147) which spontaneously cyclised to give the unstable bicyclic ring system (148).

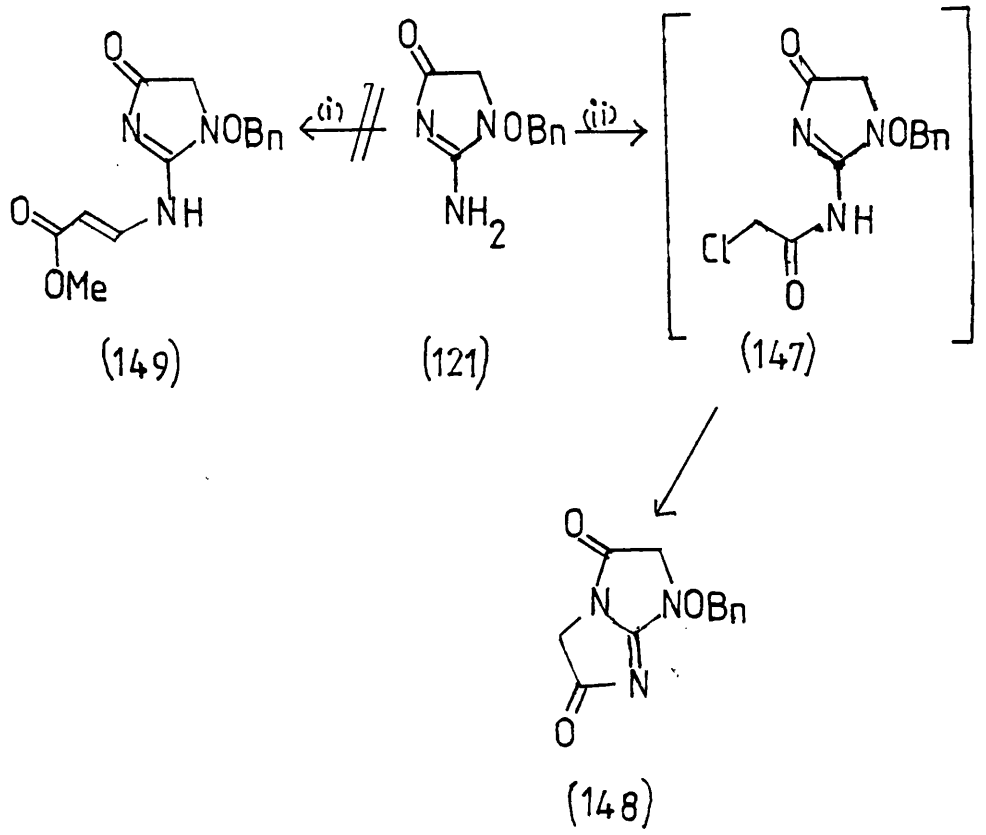
The bicyclic ring system (148) decomposed in less than one hour when stored in a fridge under nitrogen. Complete characterisation was therefore not possible.

The compound (148) exhibited two methylene proton signals at 3.20 and 3.50 δ in the H^1 Nmr spectrum and C^{13} Nmr data consistent with two methylene carbons, an imine carbon and two carbonyl carbons.

Two carbonyl streching frequencies at 1700 and 1690 cm^{-1} and an imine streching frequency at 1670 cm^{-1} were observable in the i.r. spectrum. A low resolution mass spectrum molecular ion at $^{m}/e$ 245 was obtained.

In an attempt to prepare the possible diaza prostaglandin intermediate (149) reaction of (121) with methyl propiolate resulted in a plethora of products.

Scheme 66



(149) (121) (147) (148)

Reagents

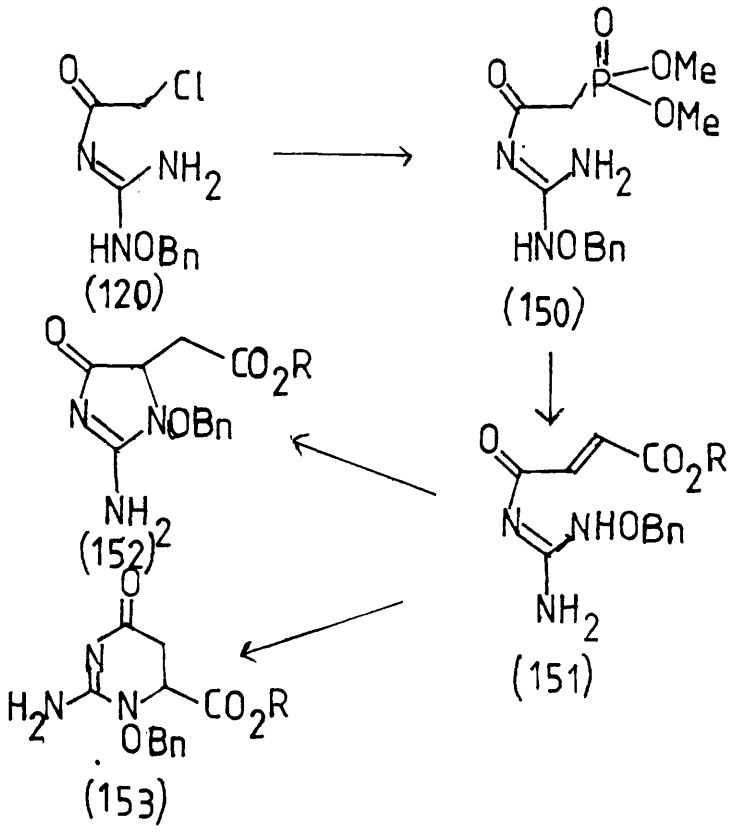
(i) $HC \equiv C - CO_2Me$, THF, Δ.

(ii) $ClCH_2COCl$, THF, Δ.

8.9 Arbuzov Reaction on 2-benzyloxy-1-Chloroacetylguanidine (120)

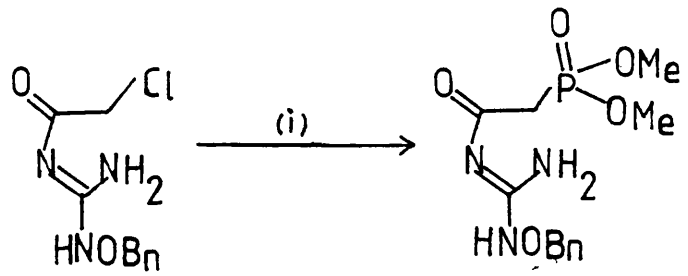
A synthetic strategem involving an Arbuzov Reaction on (120) followed by a Horner Emmons annulation to give either the imidazoline (152) or 5,6-dihydropyrimidine (153) was investigated.

Scheme 67



Reaction of (120) with neat trimethylphosphite gave the desired phosphonic ester (150). Yields in this reaction were too low (18%) to be of any further synthetic value.

Scheme 68



(120) (150)

Reagents

(i) $P(OMe)_3$, Δ, 3 days.

8.10 Conclusions

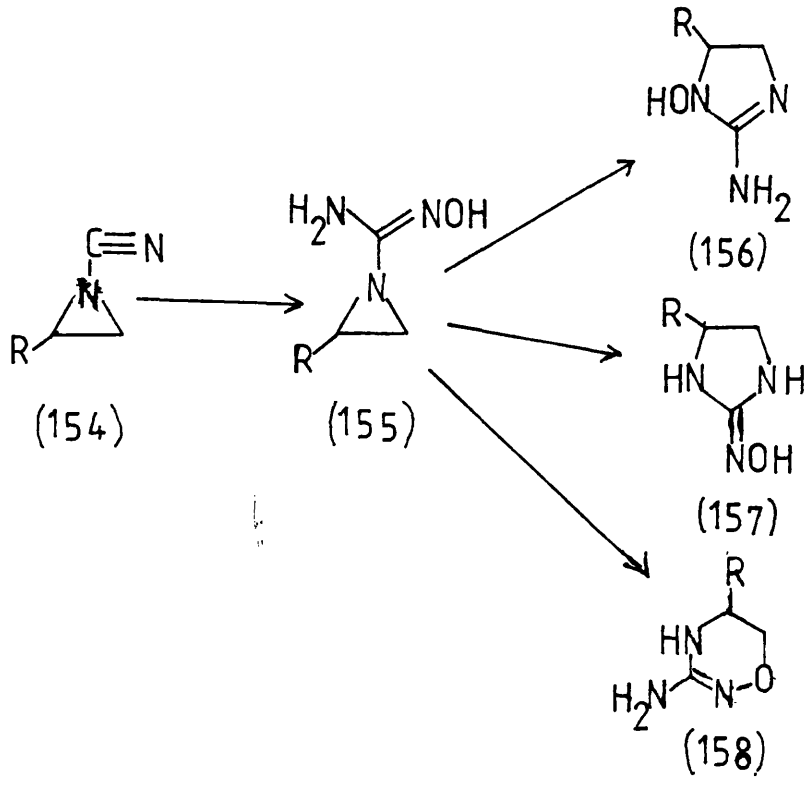
A versatile and new synthetic method for the synthesis of 1-N-hydroxy 1-N-benzyloxy hydantoins and derivatives has been developed. This method may be extended to include lipophilic alkyl groups in position C-5. Although two cyclisation modes were theoretically feasible only one was in practice observed.

9 Synthesis of 2-amino-1-hydroxy-5-phenyl-2-imidazoline

9.1 Synthetic Strategy

This section will describe a completely new synthetic entry to N-hydroxy imidazolines involving the ring expansion of aziridine-1-carboxamide oximes prepared from 1-cyanoaziridines (154) to either 2-amino-1-hydroxy-2-imidazoline (156) or 2-imino-1-hydroxy-imidazolidine(157). Other cyclisation modes were also anticipated.

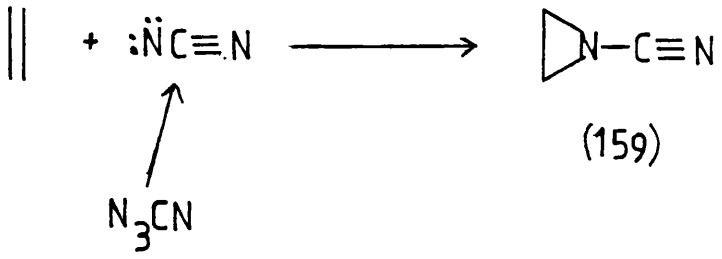
Scheme 69



9.2 Attempted Formation of 1-cyanoaziridine

1-Cyanoaziridine (159) has been prepared by addition of cyanonitrene (generated from cyanogen azide) to ethene [57]. Yields, however, were low (15%) and in view of the hazardous properties of cyanogen azide possible alternative routes were investigated.

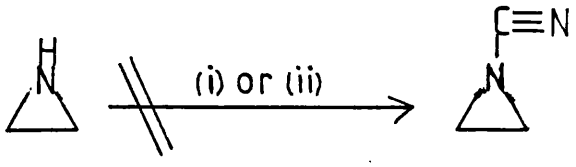
Scheme 70



(159)

On the addition of cyanogen bromide to aziridine in calcium carbonate and water no reaction occurred (i.r. monitoring of the cyanogen bromide). Additionally, the more reactive lithium aziridine was prepared and added dropwise to a solution of cyanogen bromide, resulting in an intractable mixture.

Scheme 71



(159)

Reagents

(i) CNBr, $CaCO_3$, H_2O.

(ii) MeLi, CNBr.

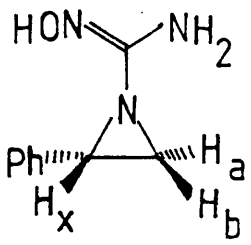
9.3 Preparation of 2-Phenylaziridine-1-carboxamide oxime

In view of the know instability of 1-cyanoaziridine (159) [57] the slightly more stable 1-cyano-2-phenylaziridine (161) was prepared by a method similar to that of Ponsold [58].

1-Cyanamino-1-phenyl-2-bromo ethane (160) was prepared by photochemical reaction of N-bromosuccinimide and cyanamide with styrene. The absence of light gave a slower reaction and a lower yield with more side products. The possible formation of 1-phenyl-1-bromo-2-cyanamino ethane could be discounted on the basis of nmr data.

Ring closure of (160) to 1-cyano-2-phenylaziridine (161) was effected by sodium hydride in THF. Compound (161) was unstable in the free state. Removal of the solvent from a solution of (161) left an intractable mixture. Consequently (161) was generated in-situ as a solution in THF and a solution of crystalline hydroxylamine added dropwise immediately to give 2-phenylaziridine-1-carboxamide oxime (162). Aziridine (162) was not isolated in the pure state, all attempts to stabilise it failing. Aziridine (162) decomposed on silica and alumina and all attempted acid salt formations (hydrochloride, malate and p-toluene sulphonate) gave inseparable mixtures. Similarly, reaction of (162) with p-nitrobenzoyl chloride and acetylation resulted in a plethora of products. An attempt to methylate aziridine (162) with diazomethane returned starting material and a small amount of polymeric material.

Aziridine (162) exhibited i.r. bands at 3590 cm (O-H str) 3510 and 3400 cm^{-1} (N-H str) characteristic of hydroxyguanidines [36] and in the nmr spectrum three-spin abx multiplets with coupling constants characteristic of 3 membered rings [59].



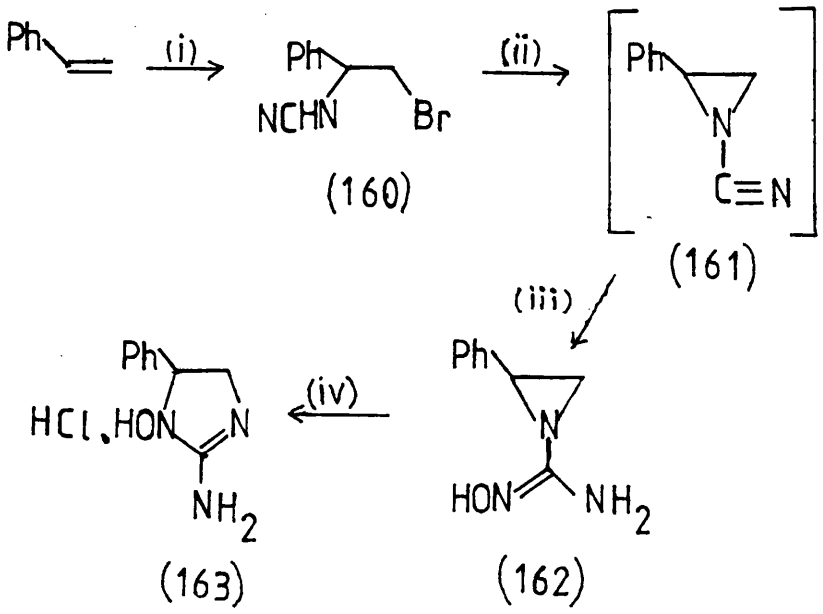
(162)

Coupling Constants for Three Membered Ring System

System	Literature Expected J values Hz	Observed J values for (162) Hz (±0.05 Hz)
Jax (trans)	6.12	6.70
Jbx (cis)	3.30	3.90
Jab (gem)	0.87	0.55

Ring expansion of aziridine (162) with triethylamine hydrochloride in refluxing acetonitrile gave 2-amino-1-hydroxy-5-phenyl-2-imidazoline hydrochloride (163). Initial attempts with sodium iodide in acetone returned starting materials whilst 18-crown-6, potassium iodide and benzene gave a very polar inseparable mixture.

Scheme 72



Reagents

(i) NBS, NH_2CN, CH_2Cl_2, $h\gamma$.

(ii) NaH, THF.

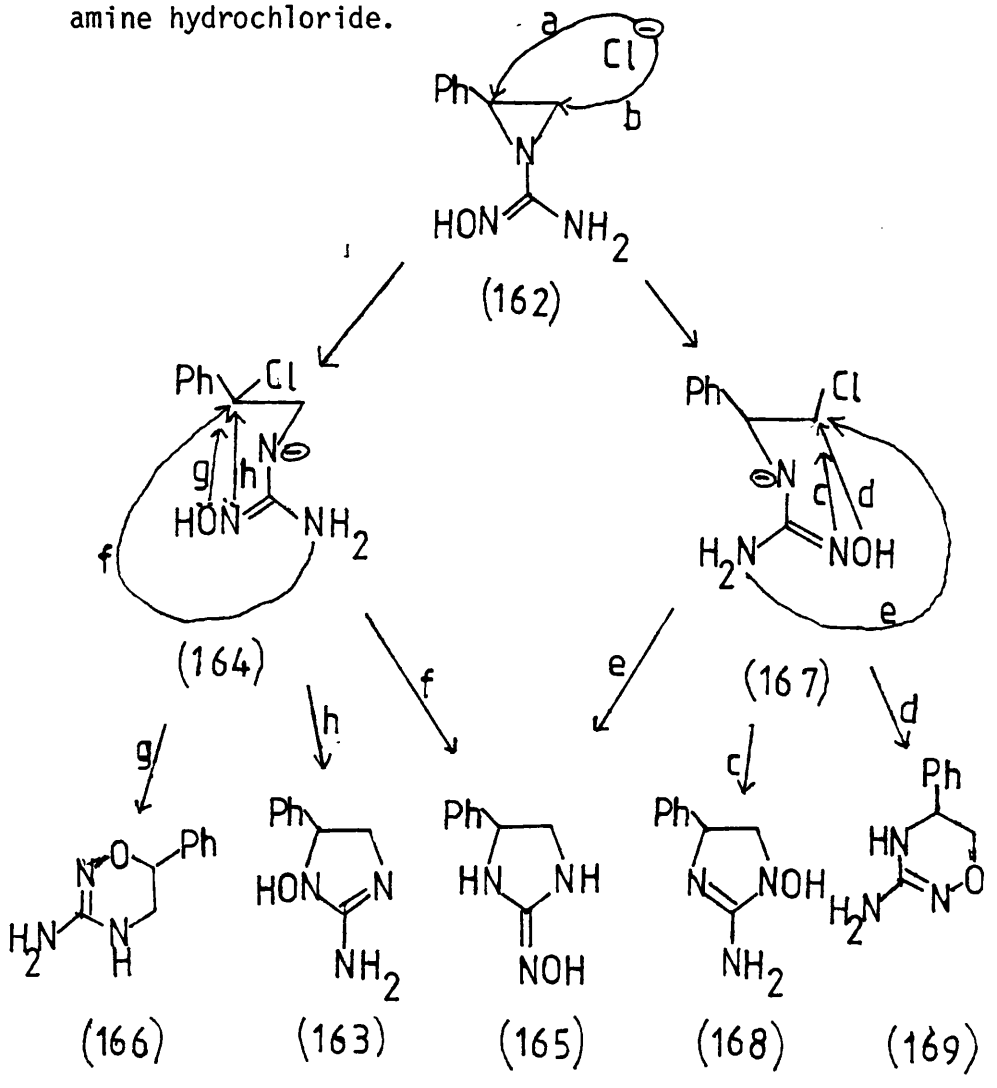
(iii) NH_2OH, THF.

(iv) $NEt_3.HCl$, MeCN.

The ring expansion of aziridine (162) presumably proceeds as indicated in Scheme 73. The possible formation of structures (165), (166), (168) and (169) may be eliminated through the presence of the fragments C_7H_7NO and C_7H_7N in the high resolution mass spectra of the acetyl derivatives (170) to (172).

Scheme 73

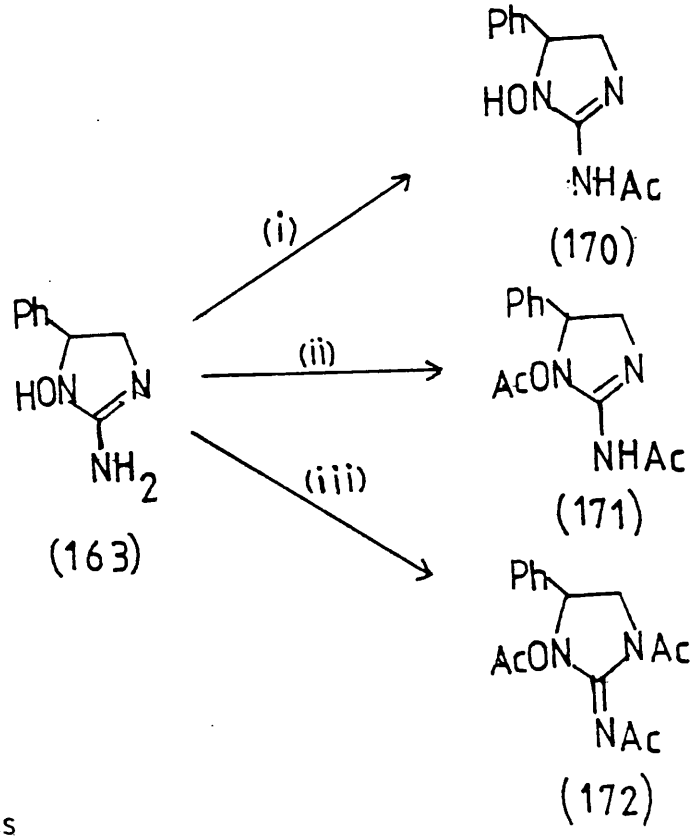
Possible products from ring expansion of (162) with triethylamine hydrochloride.



Acetylation of (163) was conducted with one, two and three molar equivalents of acetic anhydride and pyridine resulting in the formation of the mono, bis and tris acetyl derivatives (170), (171) and (172) respectively.

The mono acetyl derivative (170) exhibited an i.r. absorption band at 1670 cm^{-1} characteristic of an amide and the bisacetyl derivative (171) exhibits an additional band at 1810 cm^{-1} characteristic of an oxy-carbonyl. The triacetyl derivative (172) contained absorptions at 1810 cm^{-1} and 1670 cm^{-1}.

Scheme 74



Reagents

(i) 1 Ac_2O, pyr.

(ii) 2 Ac_2O, pyr.

(iii) 3 Ac_2O, pyr.

All attempts to dehydrate (163) to the known imidazole (173) were unsuccessful. The following conditions were tried:-

(a) diethylaminomethylpolystyrene, room temperature and reflux;

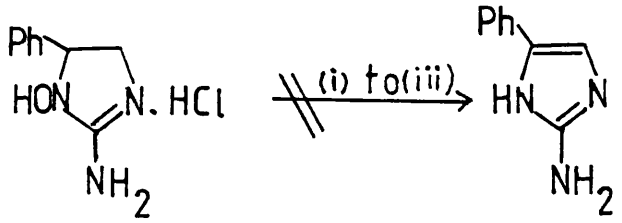
(b) triethylamine and Resin-15;

(c) diethylaminomethylpolystyrene and Resin-15.

In general, base was used to remove the hydrogen chloride from (163) and acid to effect dehydration. Solid acid and bases were used in order to prevent reaction between the two.

In all cases no reaction occurred at room temperature with the return of starting material, and heating to temperatures greater than 60° gave very polar inseparable mixtures.

Scheme 75



(163) (173)

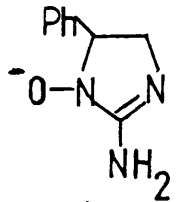
Reagents

(i) diethylaminomethylpolystyrene, RT and Δ.

(ii) NEt_3 and Resin-15.

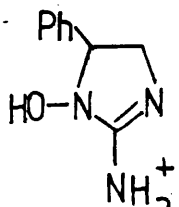
(iii) diethylaminomethylpolystyrene and Resin-15.

A possible explanation is that base gives the stable oxyanion (174).



(174)

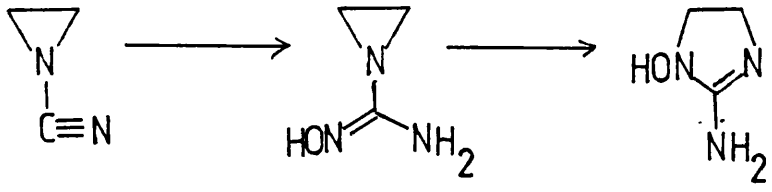
whereas acid may give stable salts:



(175)

A second synthetic strategem has therefore been devised for N-hydroxy imidazolines. The strategem invokes the synthesis of unstable 1-cyanoaziridine (176) intermediates and their reaction with hydroxylamine to give aziridine-1-carboxamide oxime (177). Ring expansion of the aziridine then gives a novel route to N-hydroxy imidazolines (178).

Scheme 76



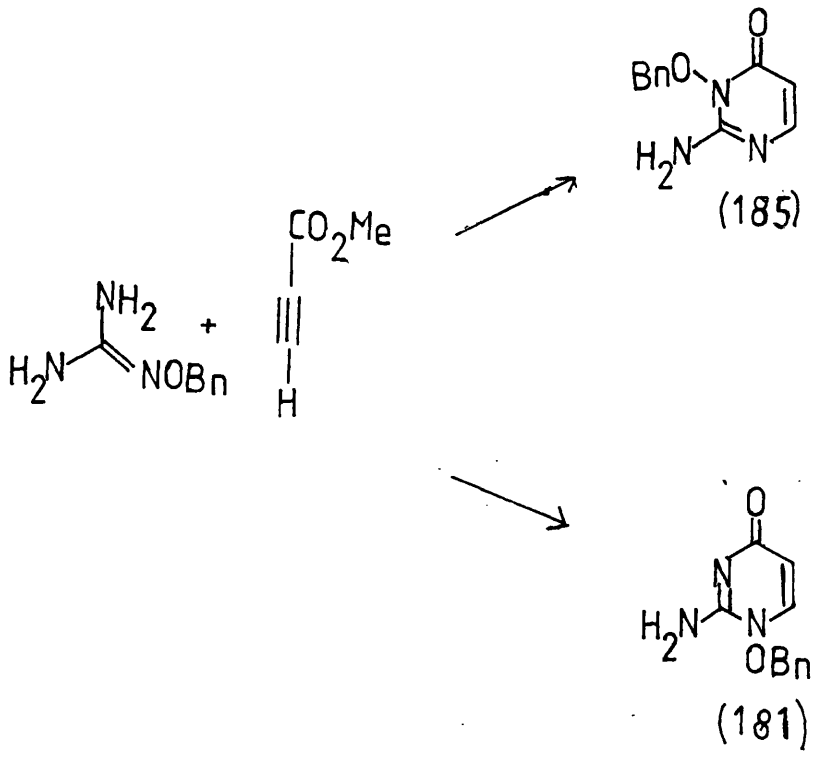
(176) (177) (178)

10 Ring Annulation Chemistry of 2-Benzyloxyguanidine and Methyl Propiolate

10.1 Synthetic Strategy

In the light of success in making five-membered ring heterocycles, it was pertinent to extend the studies and attempt to prepare six-membered ring variants. To this end, a synthetic strategem involving (a) Michael attack by the oxybenzylimino (manifestation of alpha effect) followed by (b) attack by an amino group on the ester or alternatively (a) attack by the oxybenzylimino group on the ester followed by (b) Michael addition of an amino group was investigated.

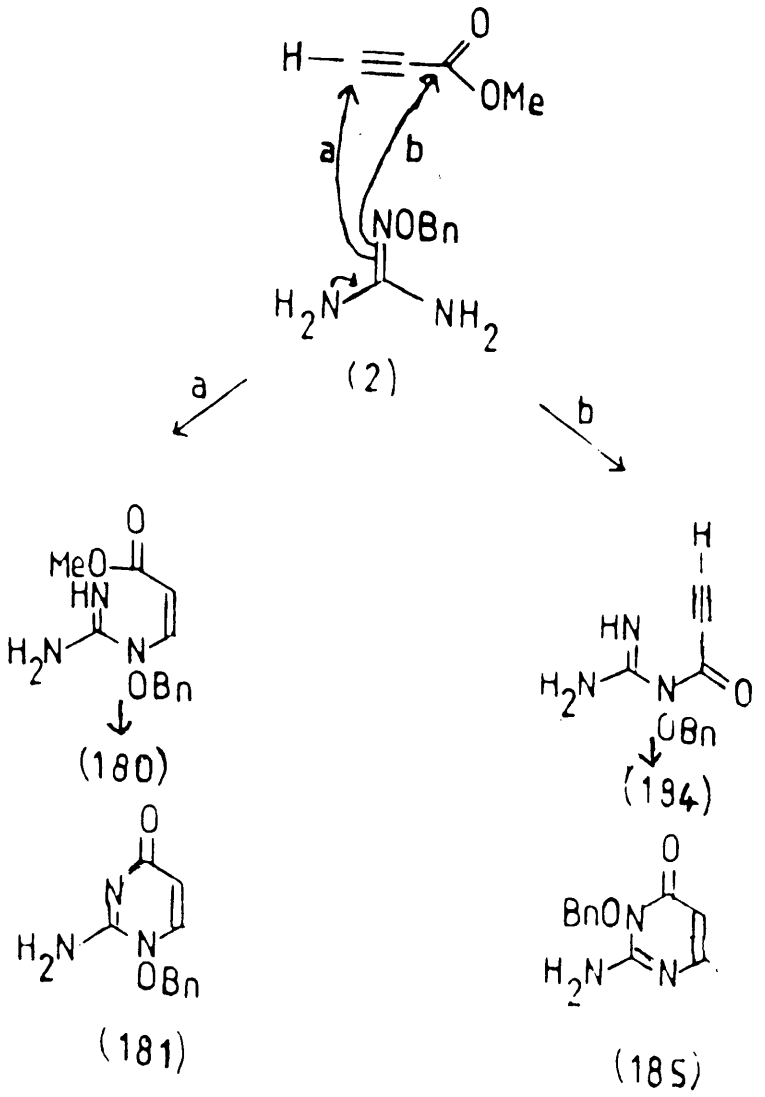
Scheme 77



A mechanistic interpretation of the possible course of chemical events may be followed in Scheme 78.

Scheme 78

Possible Mechanistic Pathways for Reaction of Benzyloxyguanidine (2) with Methyl Propiolate.



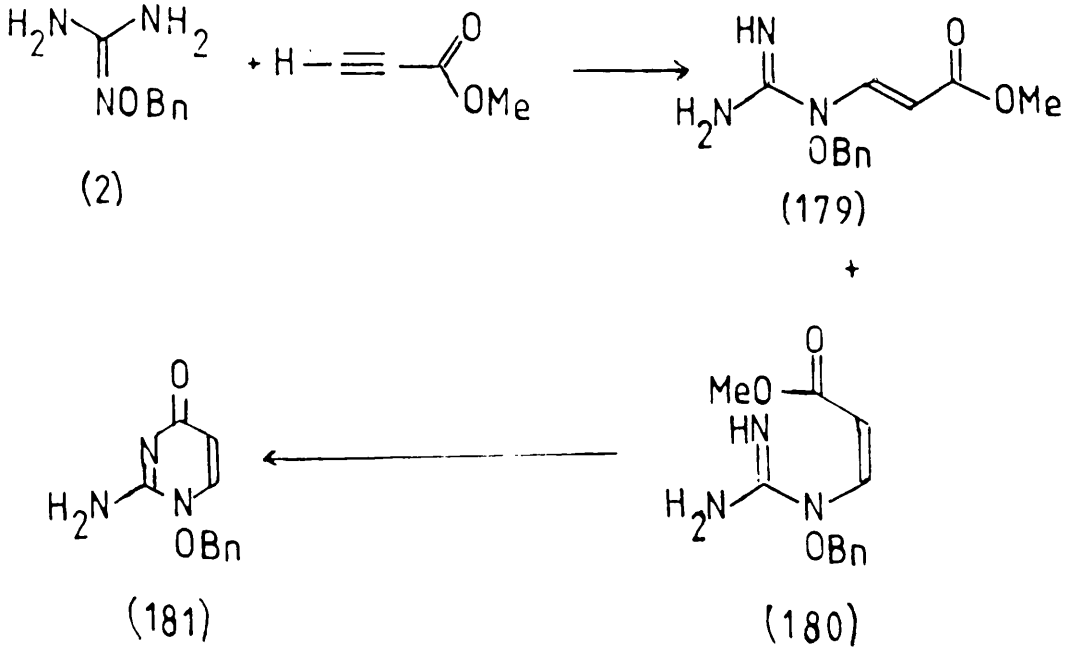
10.2 Synthesis of 2-Amino-1-hydroxy-4-pyrimidone

Reaction of 2-benzyloxyguanidine (2) with methyl propiolate results in the formation of 2-amino-1-benzyloxy-4-pyrimidone (181) in 60 yield and (Z)-methyl-3-(2[1]-benzyloxyguanidino)-2-propenoate (179) in 20% yield.

An X-ray structure proof was obtained for (181) because isomeric structure (185) could not unambiguously be precluded (Scheme 78).

It is important to note that as (181) was formed rather than (185), a possible order of chemical events was (s) Michael attack by the oxybenzylimino (manifestation of the alpha effect) to give a mixture of trans and cis olefins (179) and (180) respectively followed by (b) attack by an amino group in the cis olefin on the ester group.

Scheme 79



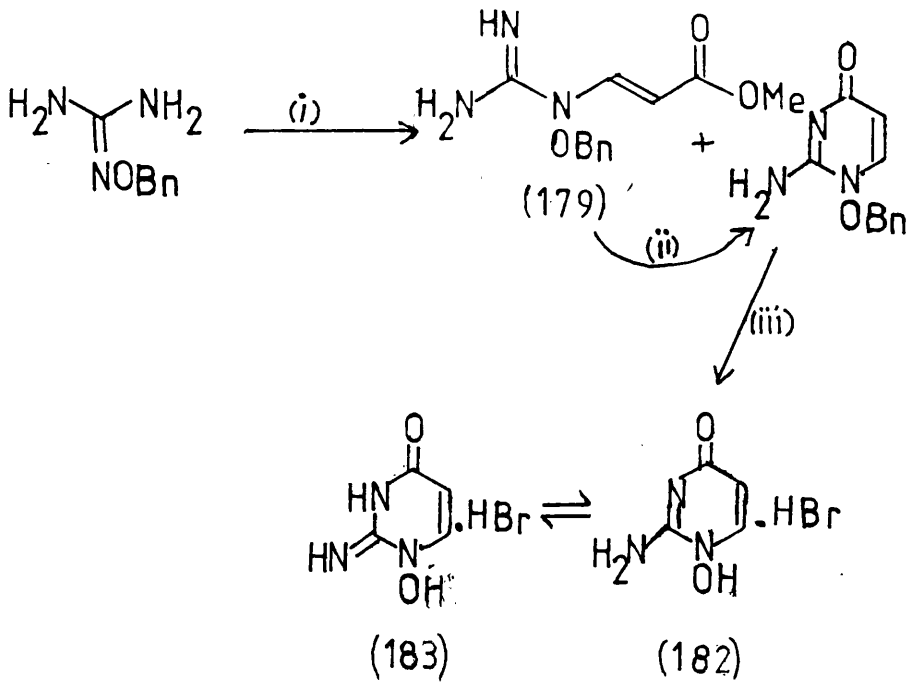
Trans olefin (179) may be converted to the cis isomer (180) and then to pyrimidone (181) by stirring a THF solution of (179) over silica for 3 days.

Debenzylation of pyrimidone (181) was successfully accomplished using excess boron tribromide in dichloromethane to give the tentatively assigned structure 2-amino-1-hydroxy-4-pyrimidone hydrobromide (182).

The presence of the tautomer 1-hydroxy-2-imino-4-pyrimidone hydrobromide (183) is also suggested by the presence of an amide carbonyl stretching frequency at 1701 cm^{-1} in the i.r. spectrum. The possible presence of any N-oxide structures may be eliminated on the basis of an unchanged C-6 C^{13} nmr signal after debenzylation. The presence of an N-hydroxy compound is further suggested by the appearance of a deep blue colour in aqueous solutions of ferric chloride.

It is thus likely that a tautomeric equilibrium of N-hydroxy structures (182) and (183) exists. On the basis of conjugation, 2-amino-1-hydroxy-4-pyrimidone hydrobromide (182) should predominate.

Scheme 80



Reagents

(i) H-C≡C-CO_2Me, THF, 0° ⟶ RT.

(ii) Silica, THF, 3 days, RT.

(iii) BBr_3, CH_2Cl_2 -78°.

Similarly, by reaction of 2-benzyloxyguanidine (2) with DMAD, 2-amino-1-benzyloxy-6-carbomethoxy-4-pyrimidone (187) was prepared.

Structure (189) may be eliminated on the basis of H^1 Nmr evidence. The aromatic protons have chemical shifts of 7.4δ (Integral 3 H) and 7.6 δ (Integral 2H). This large chemical shift difference is presumably due to anisotropic effects between the aromatic protons and the carbomethoxy group.

Anisotropic Effect Between Aromatic and Carbomethoxy Group in 2-Amino-1-benzyloxy-6-carbomethoxy-4-pyrimidone.

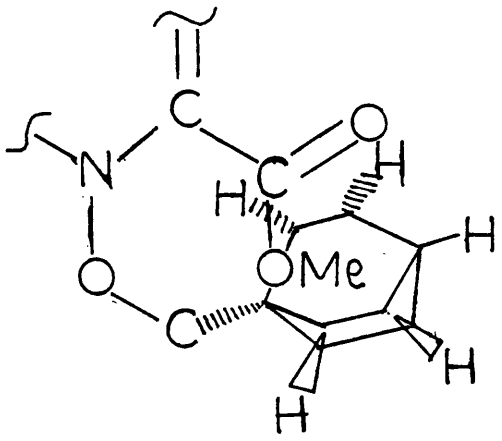
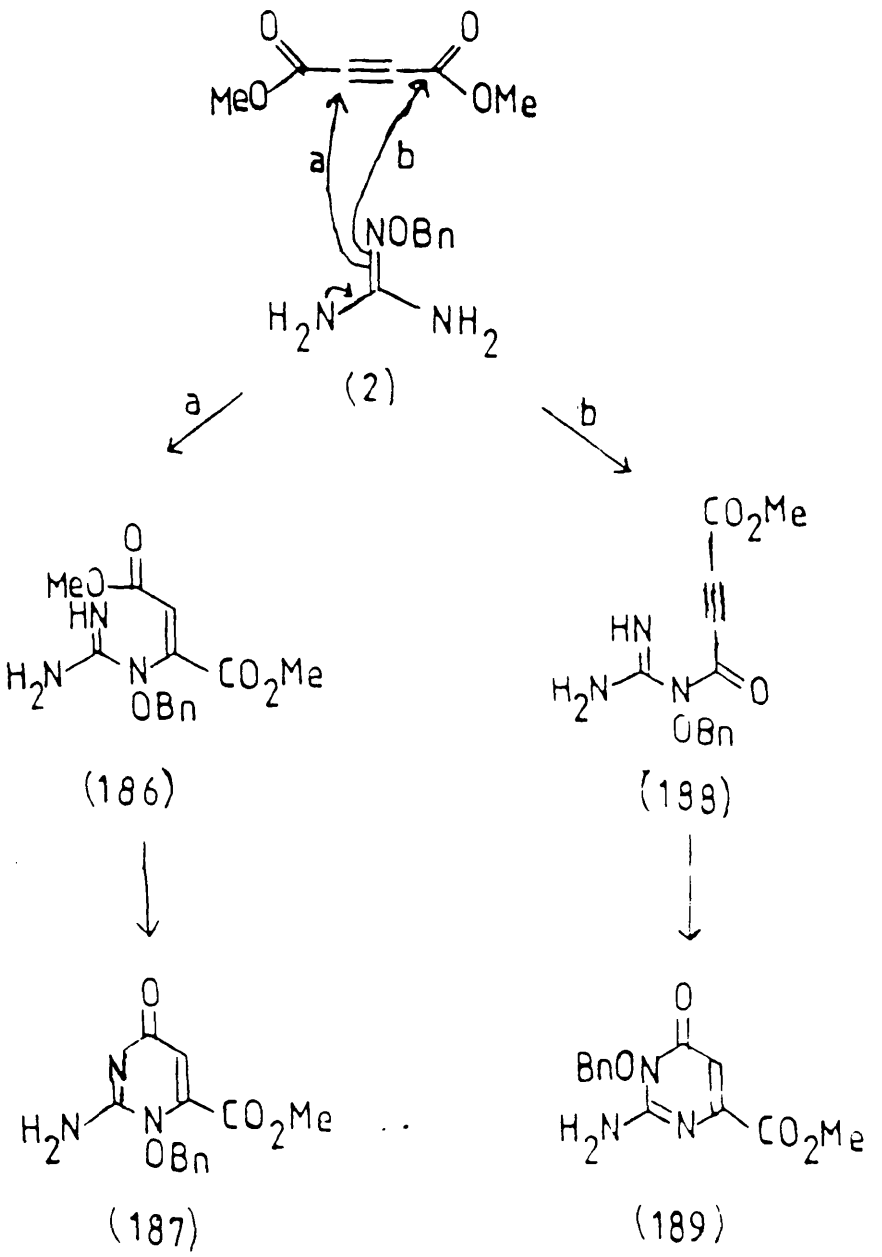


Fig 14

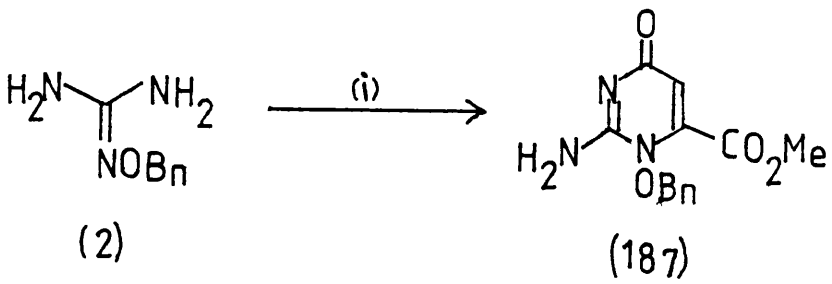
Scheme 81

Possible Mecnanistic Pathways for Reaction of 2-Benzyloxy-guanidine with DMAD.



The probable course of chemical events is as indicated in Scheme 81 with (i) Michael attack by the oxybenzylimino group (manifestation of the alpha effect) followed by (ii) attack of an amino group on the ester.

Scheme 82



(2) (187)

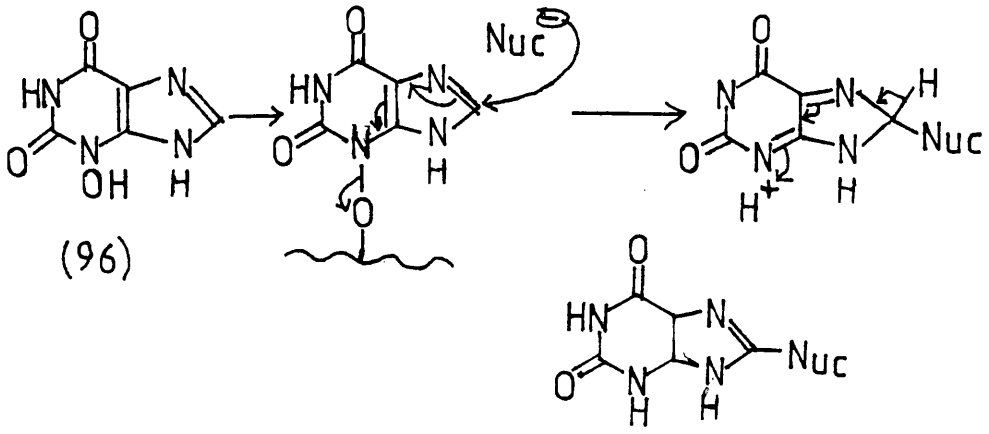
Reagents

(i) DMAD, THF $0^{\circ} \longrightarrow$ RT.

A novel synthetic strategem to 2-amino-1-hydroxy-4-pyrimidones has thus been developed involving reaction of 2-benzyloxyguanidine (2) with acetylenic esters. The probable reaction pathway involves (i) Michael attack by oxybenzyl group of (2) on the acetylenic group followed by (ii) attack by an amino group on the ester.

It is reasonable to anticipate that 2-amino-1-hydroxy-4-pyrimidones may exhibit oncogenic activity similar to 3-hydroxypurines. The oncogenic activity of 3-hydroxyxanthine (96) is explicable if (96) is converted in vivo to an ester with reactivity similar to that of 3-acetoxyxanthine (97) as discussed in Section 6.3.

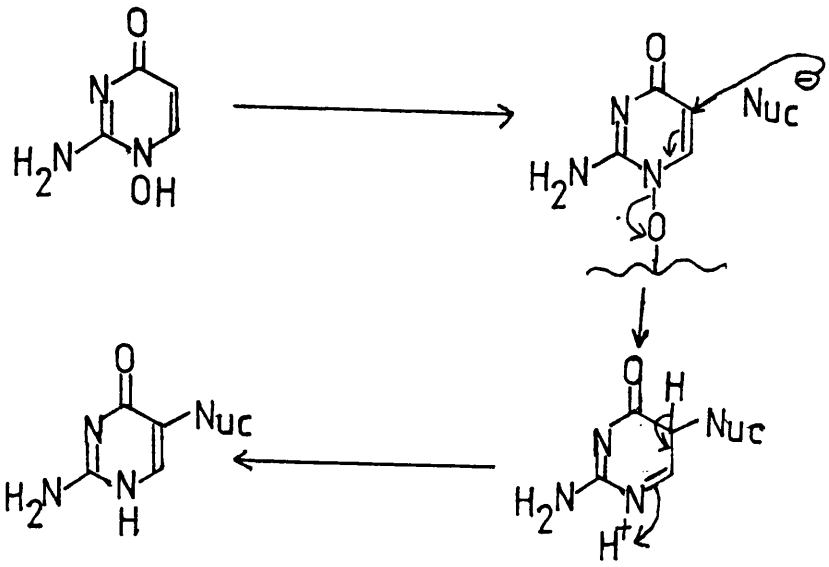
Scheme 83



(96)

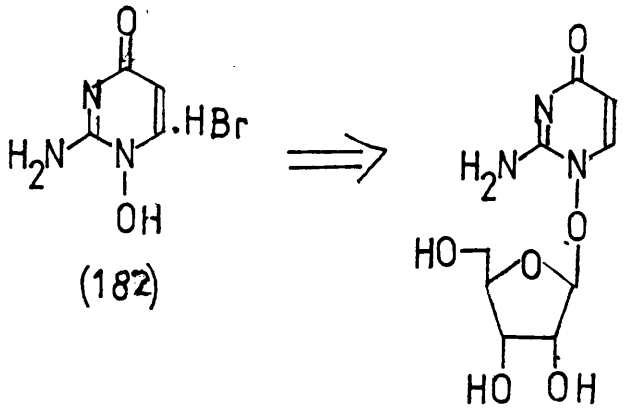
A similar mechanism may be invoked for 2-amino-1-hydroxy-4-pyrimidones.

Scheme 84



10.3 Attempted Formation of Glycosides from 2-amino-1-hydroxy-4-pyrimidone hydrobromide (182)

The following attempted ether linkages to pyrimidone (182) were made. In general the target was the linkage of R = ribofuranose to give (197).



(182)

(197)

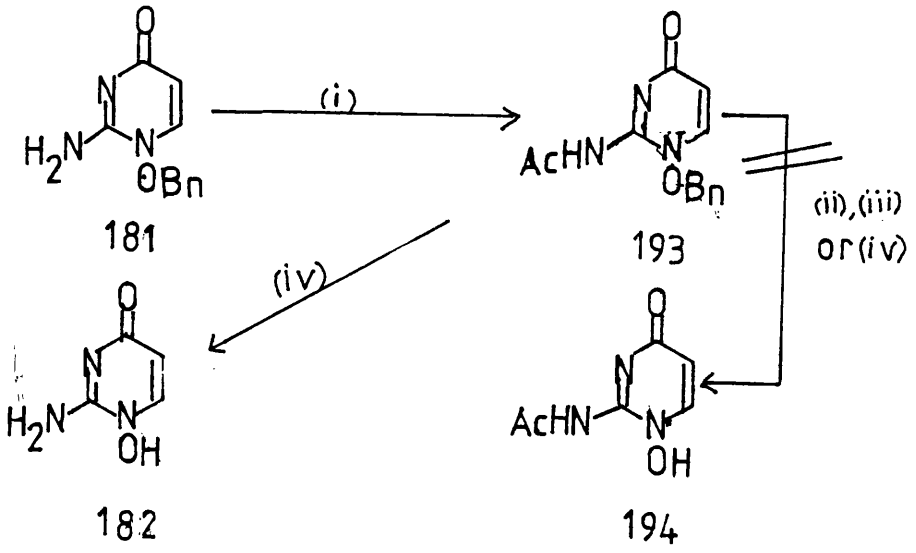
Fig 17

10.3.1 By Acetylation and Debenzylation of 2-amino-1-benzyloxy-4-pyrimidone

The synthetic strategy of acetylation of pyrimidone (180) and subsequent debenzylation was attempted as outlined in Scheme 85.

Acetylation of (181) with acetic anhydride in pyridine gave 2-acetylamino-1-benzyloxy-4-pyrimidone (193). Attempts to debenzylate (193) by atmospheric hydrogenation and with trimethylsilyl-iodide gave intractable mixtures. Attempts to debenzylate with boron tribromide gave (182) with deactylation also.

Scheme 85



Reagents

(i) Ac_2O, pyr.

(ii) 1 atm H_2, 5% Pd/C.

(iii) TMSI, CCl_4.

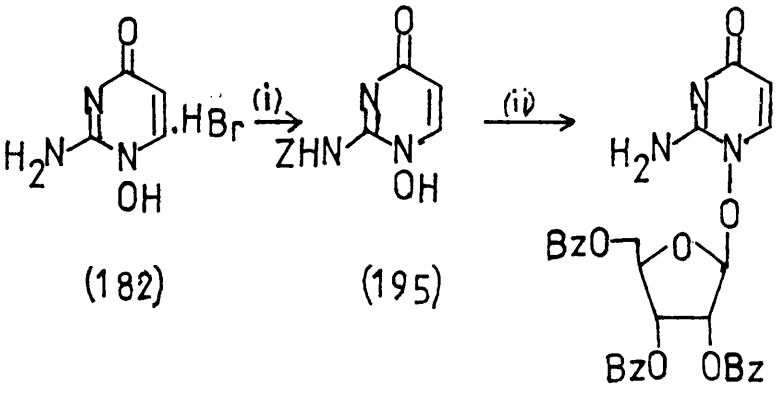
(iv) BBr_3, CH_2Cl_2.

10.3.2 By Attempted Benzyloxycarbonyl (Z) protection of 2-amino-1-hydroxy-4-pyrimidone hydrobromide

Now we come to a particularly baffling aspect of the reactivity of these 2-amino-1-hydroxy-4-pyrimidones which is not yet totally elucidated.

It was our intention to convert 2-amino-1-hydroxy-4-pyrimidone hydrobromide (182) to the benzyloxycarbonyl (Z) protected pyrimidone (195) and by reaction of (195) with a suitably protected 1-bromoribofuranose to give the glycoside (196).

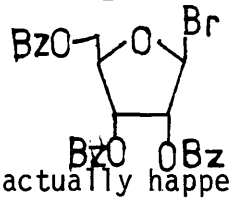
Scheme 86



(182) (195) (196)

Reagents

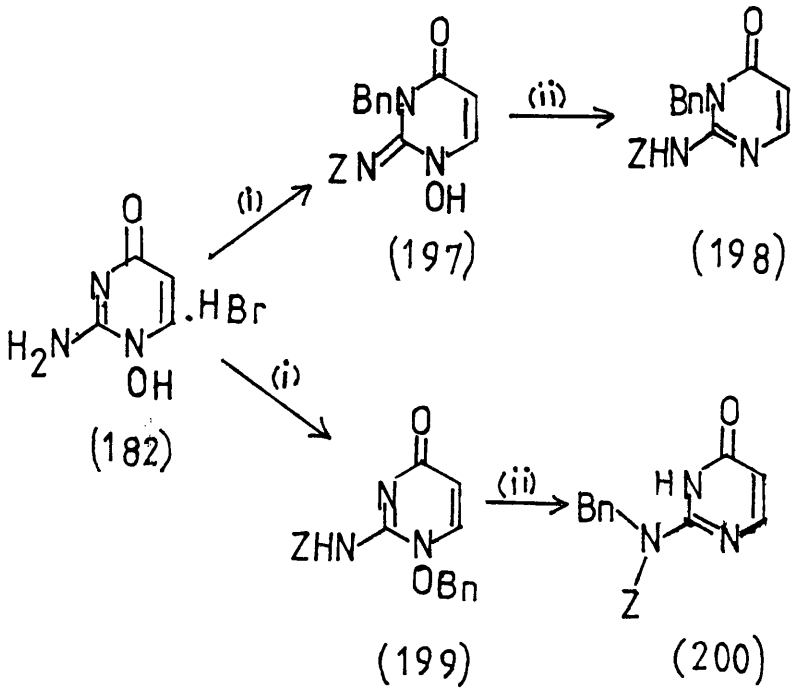
(i) $PhCH_2OCOCl$, K_2CO_3, acetone, water.

(ii) 

What actually happened was that treatment of pyrimidone (181) with benzylchloroformate gave the proposed 3-benzyl-2-benzyloxycarbonyl imino-1-hydroxy-4-pyrimidone (197) and further treatment of (197) with benzyl bromide gave the proposed 3-benzyl-2-benzyloxycarbonylamino -4-pyrimidone (198).

Other plausible structures which accommodate the spectroscopic data include (199) and (200) as outlined in Scheme 87.

Scheme 87



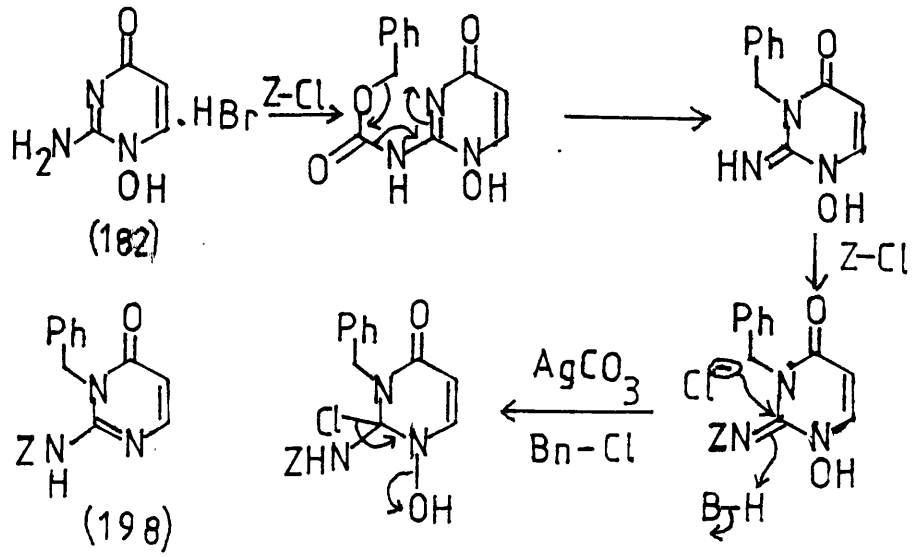
Reagents

(i) $PhCH_2OCOCl$, K_2CO_3, acetone, water

(ii) $PhCH_2Cl$, Ag_2CO_3, toluene.

A possible mechanism would be:

Scheme 88



A possible transmission of anomeric effect making N-3 more nucleophilic, facilitating the 6-membered cyclic trans benzylation with the thermodynamic liberation of carbon dioxide would account for compound (197) and by a similar mechanism compound (199). Subsequent attack of chloride ion at C-2 followed by hypochlorite elimination could explain compounds (198) and (200).

10.4 Attempted Reactions on 2-amino-1-benzyloxy-4-pyrimidone (181)

10.4.1 Attempted 5-iodination

An attempt to prepare 2-amino-1-benzyloxy-5-iodo-4-pyrimidone (201) firstly by addition of iodine across the double bond followed by elimination of hydrogen iodide gave a plethora of products.

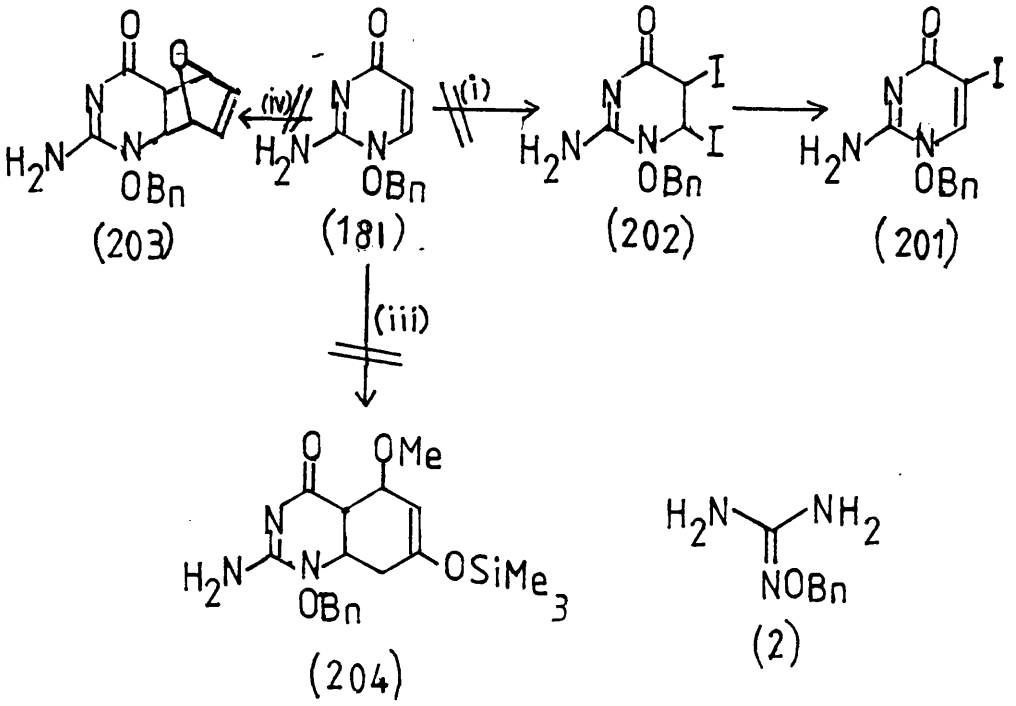
Similarly, an attempt to prepare (201) by reaction in a 3-component system with benzyloxyguanidine (2) and methyl propiolate in the presence of iodine returned starting material (2).

10.4.2 Attempted Diels-Alder Reaction

An attempted Diels-Alder reaction of (181) with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's Diene) by refluxing in toluene returned starting material. Catalytic attempts with titanium tetrachloride gave no reaction and with aluminium chloride gave an a black tar.

An attempted Diels-Alder reaction of (181) with furan thermally by refluxing in toluene returned starting material.

Scheme 89



Reagents

(i) I_2, THF, Δ.

(ii) $HC{\equiv}C\text{-}CO_2Me$, I_2, R.T.

(iii) Danishefsky's diene, toluene.

(iv) Furan, toluene.

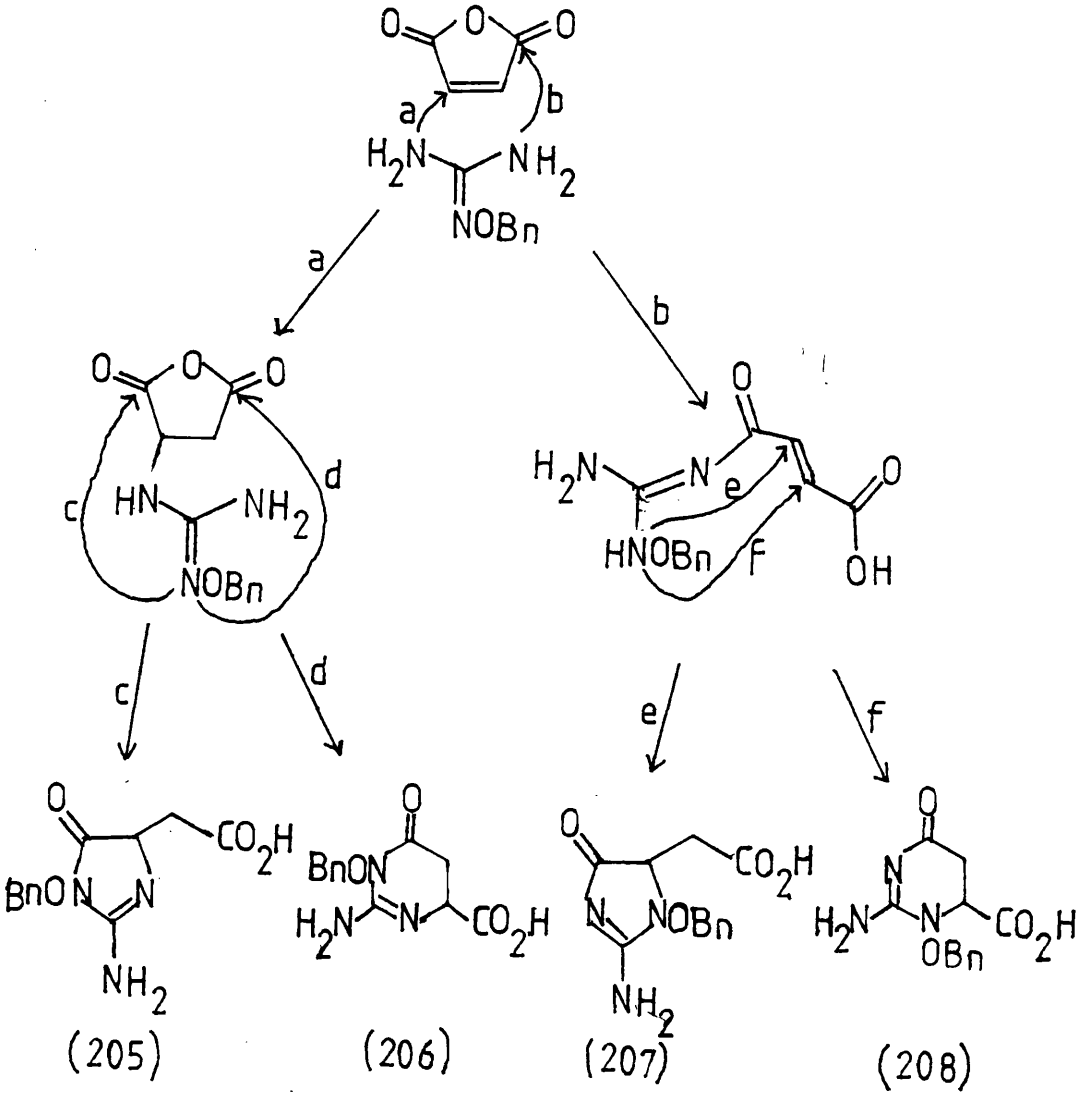
11 Ring Annulation Chemistry of Benzyloxyguanidine with Maleic Anhydride

11.1 Synthetic Strategem

Our synthetic strategem in Section 10 involved addition of benzyloxyguanidine (2) to acetylenic esters, it was therefore appropriate to extend these studies to maleic anhydride.

Four products were theoretically possible as outlined in Scheme 90.

Scheme 90



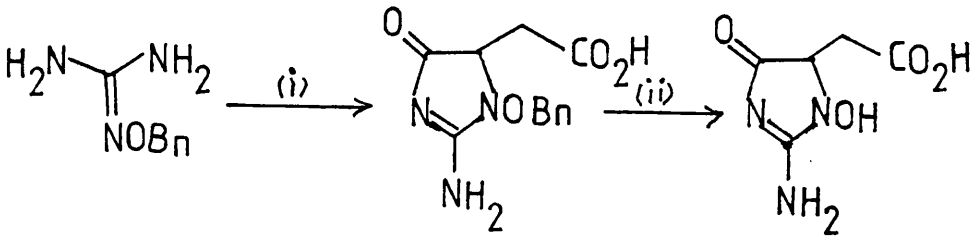
11.2 Synthesis of 2-Amino-1-hydroxyamino-4-oxo-2-imidazoline-5-ethanoic acid

Reaction of benzyloxyguanidine (2) with maleic anhydride in THF gave 2-amino-1-benzyloxy[illegible]-4-oxo-2-imidazoline-5-ethanoic acid (207). Structures (205), [illegible] and (206) can be eliminated through the presence of a u.v. chromophore in the product identical to that for (121).

The reaction product exhibits an i.r. similar to (121) and consequently (207) is favoured over structure (208).

After initial unsuccessful attempts with boron tribromide and trimethylsilyl iodide debenzylation was successfully accomplished by catalytic atmospheric hydrogenation to give 2-amino-1-hydroxyamino-4-oxo-2-imidazoline-5-ethanoic acid (209). Although slightly impure, structure (209) is consistent with i.r., u.v. and ^1H nmr data.

Scheme 91



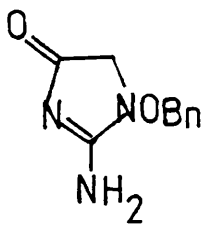
(2) (207) (209)

Reagents

(i) Maleic anhydride, THF.

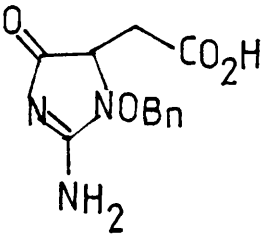
(ii) 1 atm H_2, 5% Pd/C, MeOH.

Of Structures



(121)

and



(207)

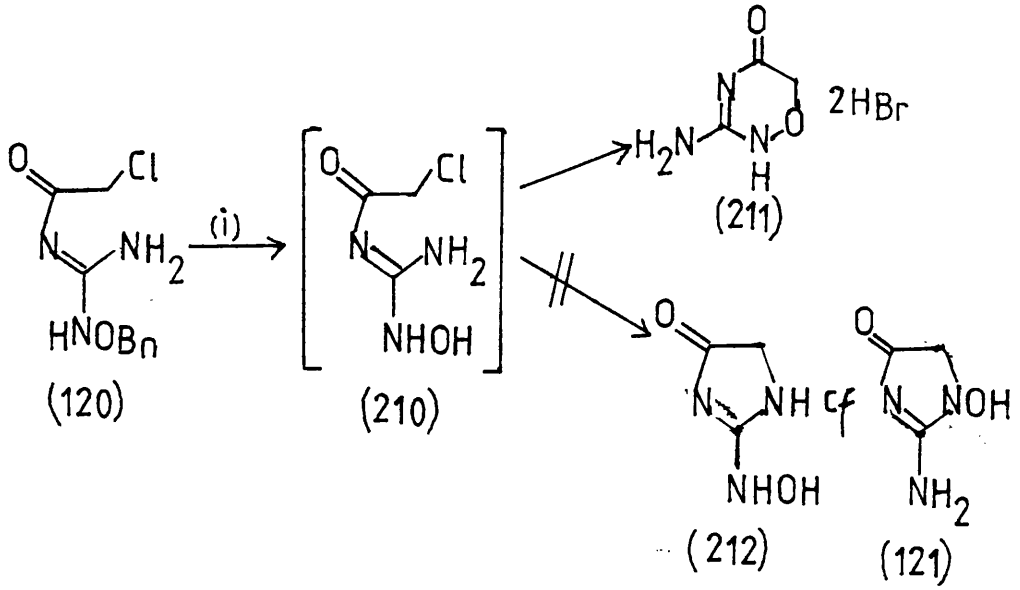
A second method for the synthesis of 1-N-hydroxy and 1-N-benzyloxy hydantoins containing the synthetically useful ethanoic acid unit at C-5 has therefore been developed, complementing and extending our earlier studies.

12 Synthesis of 3-amino-1,2,4-oxadiazine-5-one (211)

After initial unsuccessful attempts with trimethylsilyl iodide and atmospheric hydrogenation, debenzylation of 2-benzyloxy-1-chloroacetylguanidine (120) was successfully accomplished using 2 mol excess of boron tribromide to give the intermediate (210) which spontaneously cyclised to give (211).

Compound (211) has been characterised on the basis of ^1H Nmr, and analysis figures. Structure (212) may be eliminated on the basis of C-5 methylene ^1H nmr signal (4.4 δ, 2H) being considerably different to that observed for imidazoline (121) (3.6 δ, 2H).

Scheme 92



Reagents

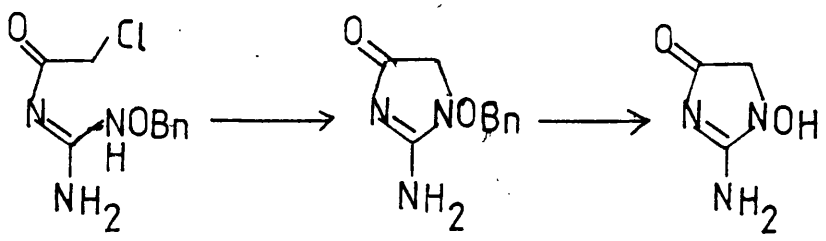
(i) BBr_3, CH_2Cl_2, -78°.

This represents yet another mode of cyclisation.

SUMMARY

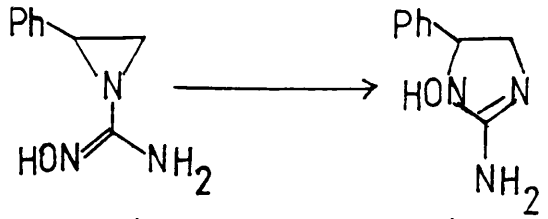
Three completely new synthetic entries to N-hydroxy imidazolines have been developed.

1) Ring closure of 2-acetylchloro-1-benzyloxyguanidine (120) to 2-amino-1-benzyloxy-4-oxo-2-imidazoline(121) followed by hydrogenation gave 2-amino-1-hydroxy-4-oxo-2-imidazoline (122).



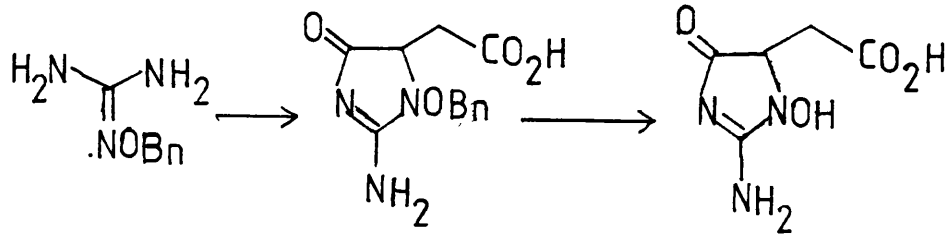
(120) (121) (122)

2) Ring expansion of 2-phenylaziridine-1-carboxamide oxime (162) gave 2-amino-1-hydroxy-5-phenyl-2-imidazoline (163).



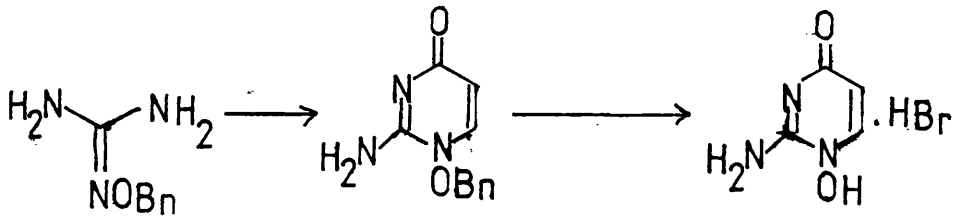
(162) (163)

3) Reaction of 2-benzyloxyguanidine (2) with maleic anhydride gave 2-amino-1-benzyloxy-4-oxo-2-imidazoline-5-ethanoic acid (207). Hydrogenation of (207) afforded 2-amino-1-hydroxy-4-oxo-2-imidazoline-5-ethanoic acid (209).



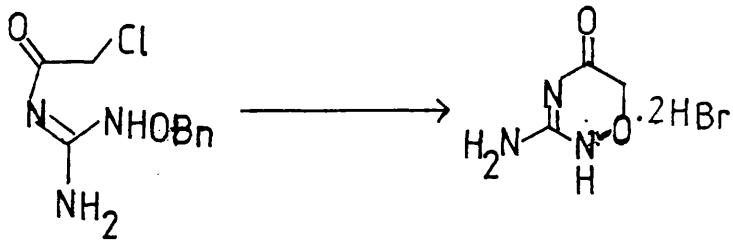
(2) (207) (209)

A new synthetic route to 2-amino-1-hydroxy-4-pyrimidones has also been developed. Reaction of 2-benzyloxyguanidine (2) with methyl propiolate gave 2-amino-1-benzyloxy-4-pyrimidone (181). Debenzylation with boron tribromide gave 2-amino-1-hydroxy-4-pyrimidone hydrobromide (182).



(2) (181) (182)

Finally, reaction of boron tribromide on 2-chloroacetyl-1-benzyloxy-guanidine (120) gave by yet another mode of cyclisation, 2-amino-1,2,4-oxadiazine-5-one dihydrobromide (211).



(120) (211)

EXPERIMENTAL

EXPERIMENTAL

Mps were determined with a Kofler hot-stage apparatus. ^{1}H and ^{13}C nmr spectra were recorded on a Varian XL100 and i.r. spectra measured on Perkin Elmer 457 and 983 spectrophotometers. Elemental analysis were carried out by the Analytical R. and D. Laboratories, Organon Laboratories Limited, Newhouse and Mass Spectra run on a Perkin Elmer MS902 at Strathclyde University, Glasgow.

Liberation of 2-Methylthio-2-imidazoline (107) from its hydriodide salt

2-methylthio-2-imidazoline hydriodide (9.8 g, 40 mmol) was dissolved in the minimum of water (35 ml) at 0° and treated with an aqueous solution of potassium hydroxide {(2.3 g, 40 mmol) in water (30 ml)} at 0°. Salt was then added to saturation and the mixture extracted with ether (5 x 30 ml), dried (Na_2SO_4) and solvent removed at reduced pressure to return 2-methylthio-2-imidazoline (90) (4.1 g, 85%) (mp 102-103°, lit [60] 100-102°).

Nmr δ (DMSO-d6) 2.35 (s,3H) 3-45 (s,4H) 5.5 (broad s, 1H exch)i.r.(KBr) γ_{max} 3300-3000 broad band. 1640 (C = N str).

The compound was unstable decomposing with the liberation of methyl mercaptan and was generally used immediately.

Preparation of 2-Hydroxyamino-2-imidazolidine acetate (109) from 2-Methylthio-2-imidazoline using hydroxylamine liberated from its hydrochloride salt with triethylamine

Triethylamine (0.70 ml, 5 mmol) was added to a solution of hydroxylamine hydrochloride (0.35 g, 5 mmol) in DMF (5 ml) and the resultant triethylamine hydrochloride filtered off. To the solution of hydroxylamine in DMF was added acetic acid (0.29 ml, 5 mmol) and the mixture added to a solution of 2-methylthio-2-imidazoline (0.58 g, 5 mmol) in DMF (5 ml). The reaction mixture was heated to 50° and left to cool overnight. The solvent was then removed "in vacuo" to leave an oily residue which was dissolved in methanol and acetone added till slightly turbid. On standing for several hours crystallisation occurred and 2-hydroxyamino-2-imidazolidine acetate (89) (0.22 g, 30%) filtered off. (mp 112-114° lit 112-115°) Nmr δ(DMSO-d6) 1.80 (s,3H) 3.35 (s, 4H) 8.50 (broad s,4H, exch)i.r. γ_{max} cm^{-1} broad band 3350 (N-H str) 1690 (C = O) 1670 (C = N), ^{13}C ppm (DMSO-d6) 23.01 (CH_3) 42.50 (CH_2) 161.23 (C = N)

174.66 (C = O). Found: C,37.04; H,6.86; N,26.33; $C_5H_{11}N_3O_3$ requires C,37.26; N,6.88; N,26.33%.

Improved Synthesis of 2-hydroxyamino-2-imidazolidine acetate (109) from 2-methylthio-2-imidazoline using crystalline hydroxylamine

To a solution of 2-methylthio-2-imidazoline (1.16 g, 10 mmol) in DMF (10 ml) was added acetic acid (0.6 ml, 10 mmol) and the mixture cooled to 0°. Crystalline hydroxylamine (0.33 g, 10 mmol) was then added and the mixture stirred under nitrogen at 0° for 1 h before warming to room temperature and stirring for a further 1 h. Dioxan was added until precipitation was complete. Crystallisation from methanol-acetone afforded 2-hydroxyamino-2-imidazolidine acetate (89) (1.40 g, 94%) identical in all respects to the above compound.

Preparation of 2-Hydroxyamino-2-imidazolidine hydrochloride (110)

A solution of hydroxylamine hydrochloride (0.35 g, 5 mmol) in DMF (5 ml) was added to a cooled solution of 2-methylthio imidazoline (0.58 g, 5 mmol) in DMF 5 ml at 0°. The mixture was then warmed to room temperature and dioxan added until precipitation was complete and 2-hydroxyamino imidazolidine hydrochloride (91) (from methanol) filtered off. (0.66 g, 96%) mp (171-175° lit 166-168°) Nmr δ(broad s, 2H, exch.) i.r. ν_{max} cm^{-1} 3300-2500 (broad band) 1670 (C = N str). Found: C,26.40; H,5.97; N 30.62; Cl 25.57; $C_3H_8N_3Cl$ O requires C,26.19; H,5.86; N,30.54; Cl 25.77%.

Attempted Formation of 2-Hydroxyamino-2-imidazolidine hydriodide (111)

To a stirred suspension of 2-methylthio-2-imadazoline hydriodide (2.44 g, 10 mmol) in dioxan (20 ml) was added crystalline hydroxylamine (0.33 g, 10 mmol) in dry distilled dioxan (10 ml) dropwise over 5 min under nitrogen.

The mixture was then left to stir at room temperature. After 2 h tlc indicated no reaction. Consequently the mixture was brought to reflux under nitrogen. After 6 h tlc again indicated no reaction. The reaction mixture was thus cooled to room temperature and starting material (2.41 g) filtered off.

Preparation of 2-Methylthio-4-oxo-2-imidazoline hydriodide (113)

Thiohydantoin (2.28 g 20 mmol) was suspended in methanol (5 ml) and methyl iodide (1.56 ml, 24 mmol) added and the mixture refluxed for 2 h. On cooling 2-methylthio-4-oxo-2-imidazoline hydriodide (93) (from methanol-ether) (4.92 g, 96%) was filtered off mp 158-160°. Nmr δ(DMSO-d6) 2.55 (s, 3H), 4.30 (s, 2H) 7.20 (Broad s, 2H exch). i.r.(KBr) ν_{max} cm^{-1} 3300-2500 broad band 1680 (C = O str) 1670 (C = N str).

Liberation of 2-Methylthio-4-oxo-2-imidazoline (108) from its hydriodide salt

(2-methylthio-4-oxo-2-imidazoline hydriodide (2.54 g, 10 mmol)) was dissolved in the minimum of water (8 ml) cooled to 0° and treated with an ice cooled solution of potassium hydroxide (0.56 g, 10 mmol in 5 ml water). Salt was added to saturation and the mixture extracted immediately with ether (5 x 10 ml) dried (Na_2 SO_4) and solvent removed to return 2-methylthio-4-oxo-2-imidazoline (94) (0.4 g, 30%). Nmr δ(DMSO-d6) 2.45 (s, 3H) 4.00 (s, 2H) 5.40 (s, 1H, exch) i.r.(KBr) ν_{max} cm^{-1} 3320 (N-H str) 1680-1660 (C = O and C = N str). No further purification was attempted and the compound was used immediately.

Attempted Liberation of 2-Methylthio-4-oxo-2-imidazoline (108) from its Hydriodide Salt using Sodium Ethoxide as Base

A solution of sodium ethoxide prepared from the addition of sodium (0.23 g, 10 mmol) to ethanol (20 ml) under nitrogen was added dropwise to a solution of 2-methylthio-4-oxo-2-imidazoline hydriodide (2.58 g, 10 mmol) in ethanol (20 ml) and the mixture left to stir for 3 min. A 10 ml aliqout was concentrated under reduced pressure and inorganic solids filtered off (40 mg). Further concentration resulted in an intractable red tar (0.65 g). To the remaining 30 ml, ether was added until precipitation occurred and the intractable solids filtered off. Evapouration of the filtrate left an intractable tar.

Attempted Preparations of 2-Hydroxyimino-4-oxo-2-imidazoline

(a) As the Hydrochloride Salt (114)

(i) Addition of Hydroxylamine hydrochloride to (108) using DMF as solvent

Thio-imidazoline (108) (1.04 g, 8 mmol) was dissolved in dry DMF (10 ml) and a solution of hydroxylamine hydrochloride (0.55 g, 8 mmol) in DMF (10 ml) added under nitrogen. After stirring at room temperature for 24 h, an aliqout was removed (5 ml), removal of the solvent under vacuum returned a red solid (0.4 g) consisting almost entirely of starting materials. The remainder was refluxed under nitrogen for 2 h to return an intractable mixture.

(ii) Addition of Hydroxylamine hydrochloridide to (108) using methanol as a solvent

A solution of hydroxylamine hydrochloride (140 mg, 2 mmol) in dry methanol (5 ml) was added to a solution of thio-imidazoline (108) (260 mg, 2 mmol) and the mixture stirred at room temperature under nitrogen for 3 days. Removal of solvent from an aliquot returned starting material.

Reflux of the remainder resulted in the formation of an intractable mixture.

(iii) By Reaction of Hydroxylamine hydrochloride on Thiohydantoin (92)

A solution of (92) (2.32 g, 10 mmol) and hydroxylamine hydrochloride (1.40 g, 20 mmol) in methanol (20 ml) was refluxed under nitrogen. After 7 days tlc indicated no reaction and removal of the solvent left starting materials.

(b) As the Free Compound (115)

(i) Addition of Hydroxylamine to (108)

To a solution of hydroxylamine hydrochloride (0.278 g, 4 mmol) in DMF (5 ml) was added triethylamine (0.55 ml, 4 mmol) and the resultant triethylamine hydrochloride filtered off. The filtrate solution of hydroxylamine was then added to a solution of thio-imidazoline (108) (0.52 g, 4 mmol) in DMF (5 ml) and the mixture left to stir overnight under nitrogen. Subsequent removal of solvent under reduced pressure from an aliquot (2.5 ml) returned starting material (0.14 g).

Reflux of the remainder returned an intractable mixture.

(ii) Addition of Crystalline Hydroxylamine to (108)

A solution of crystalline hydroxylamine (0.13 g, 4 mmol) in DMF (5 ml) was added dropwise to a solution of (108) (0.52 g, 4 mmol) in DMF (10 ml) and the solution left to stir under nitrogen for 7 days. Removal of the solvent at reduced pressure returned starting material (0.53 g).

(c) As the Acetate (116)

(i) Addition of Hydroxylamine to (108) in the Presence of Acetic Acid

Hydroxylamine hydrochloride (0.41 g, 6 mmol) was dissolved in DMF (10 ml) and triethylamine (0.83 ml, 6 mmol) added. The resultant triethylamine hydrochloride was filtered off and the hydroxylamine filtrate added dropwise to a solution of (108) (0.78 g, 6 mmol) and acetic acid (0.46 ml, 6 mmol) in DMF (10 ml) under nitrogen. The resultant mixture was stirred overnight and solvent removed at reduced pressure to return starting materials (1.58 g).

(ii) Addition of Crystalline Hydroxylamine to (108) in the Presence of Acetic acid

A solution of crystalline hydroxylamine (0.13 g, 4 mmol) in DMF (5 ml) was added dropwise to a solution of (108) (0.52 g, 4 mmol) in DMF (10 ml) and the mixture left to stir under nitrogen. After 7 days, tlc indicated no reaction, the solvent was removed *in vacuo* to leave a red solid consisting largely of starting materials.

(d) As the Hydriodide (117)

(i) Addition of Hydroxylamine to (113) in DMF

Hydroxylamine was liberated from hydroxylamine hydrochloride (0.70 g, 10 mmol) with triethylamine (1.4 ml, 10 mmol) in DMF (20 ml) filtering off the triethylamine hydrochloride. The hydroxylamine solution was added to a solution of imidazoline (113) (2.58 g, 10 mmol) in DMF (15 ml) and the misture left to stir for 12 h under nitrogen.

Tlc indicated an intractable mixture, the reaction was discarded.

(ii) Addition of Hydroxylamine to (113) in Ethanol

A 10 mmol solution of sodium ethoxide was prepared in ethanol (20 ml) and added to a solution of hydroxylamine hydrochloride (0.70 g, 10 mmol) in ethanol (20 ml). The resultant sodium chloride was filtered off and the hydroxylamine solution added to a solution of imidazoline (93) (2.58 g, 10 mmol) in ethanol. The mixture was left to stir under nitrogen. After 4 days tlc indicated no reaction and removal of the solvent *in vacuo* left largely starting material.

(iii) Addition of Crystalline Hydroxylamine to (113)

Crystalline hydroxylamine (0.13 g, 4 mmol) was added to a suspension of imidazoline (113) (1.04 g, 4 mmol) in dioxan (15 ml) and the mixture left to stir under nitrogen. After 7 days tlc indicated no reaction and removal of the solvent in vacuo left largely starting material.

Attempted Preparations of 2-Chloro-4-oxo-2-imidazoline (119)

(a) Chlorination of Thiohydantoin

Thiohydantoin (1.16 g, 10 mmol) was suspended in dichloromethane (20 ml) and pyridine (2.4 ml, 30 mmol) added. An excess of phosgene was added and the mixture stirred at room temperature adding futher phosgene occasionally. The solvent was then decanted off to leave an intractable tar.

(b) Chlorination of Hydantoin

Hydantoin (2 g) was suspended in freshly distilled phosphonyl chloride (80 ml) and the mixture brought to reflux under nitrogen. Removal of the excess phosphonyl chloride by distillation left an intractable solid.

Preparation of 2-Benzyloxyguanidine (2)

A suspension of O-benzyl hydroxylamine hydrochloride (27.1 g, 0.17 mol) and cyanamide (7.14 g, 0.17 mol) in toluene (150 ml) was refluxed for 2 days under nitrogen. The solvent was then removed to return a gum which was suspended in the minimum of water, washed with ether and 4 N sodium hydroxide added until precipitation was complete.

Filtration returned 2-benzyloxyguanidine (from ethanol) (2) (2.4 g, 85%) mp 106-7° (lit 104-7°) identical in all other respects to literature.

Formation of 2-Benzyloxy-1-chloroacetylguanidine (120)

To an ice cooled solution of 2-benzyloxyguanidine (16.5 g, 0.1 mol) and triethylamine (14 ml, 0.1 mol) in THF (150 ml) was added dropwise a solution of chloroacetyl chloride (8 ml, 0.1 mol) in THF (50 ml) under nitrogen. The reaction mixture was then allowed to warm to room temperature and poured into water (700 ml) giving a precipitate. The precipitate was filtered, washed with water and crystalised from methanol afforded 2-benzyloxy-1-chloroacetylguanidine (120) (20.5 g, 85%) (mp 130-1°). Nmr $\delta(CDCl_3)$ 3.95 (s, 2H, CH_2Cl) 4.86 (s, 2H, $PhCH_2$) 5.80-6.60 (broad s, exch) 7.31 (5H, Ph) C^{13} ppm(DMSO) 42.90 (CH_2-Cl), 74.81 (CH_2-Ph) 127.47, 127.79, 128.30, 128.80, 130.127 and 131.98 (arom) 149.62 (C = N) and 166.91 (C = O).
i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3495 and 3375 (N-H str) 1695 (C = O str) 1675 (C = N str) u.v. λ_{max} (EtOH) (nm) 214 and 249 (7331). Found: C,49.44; H,4.99; N,17.42; Cl 15.05; $C_{10}H_{12}N_3ClO_2$ requires C,49.70; H,5.00; N,17.39; Cl 14.67%.

Formation of 2-Benzyloxy-1-dichloroacetylguanidine (128)

To an ice cooled solution of 2-benzyloxyguanidine (1.65 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in THF (20 ml) was added a solution of dichloroacetyl chloride (1.0 ml, 10 mmol) in THF (5 ml) under nitrogen.

The reaction mixture was then allowed to warm to room temperature and poured into water (100 ml) giving a precipitate. The precipitate was filtered, washed with water and recrystalised from methanol to afford 2-benzyloxy-1-dichloroacetylguanidine (128) (2.3 g, 84%) mp 86-87. Nmr $\delta(CDCl_3)$ 4.85 (s, 2H, $PhCH_2$-) 5.82 (s, 1H, $CHCl_2$) 5.90-6.80 (broad s, 3H, exch) 7.40 (5H, Ph). i.r. γ_{max} (KCl) 3490 and 3380 (N-H str) 1690 (C = O str) and 1680 (C = N). u.v. λ_{max} (EtOH) nm 211 and 253 (7,540). Found: C,43.54; H,4.02; N,15.32; Cl 25.25; $C_{10}H_{11}N_3Cl_2O_2$ requires C,43.49; H,4.02; N,15.02; Cl 25.68%.

Ring Closure of 2-Benzyloxy-1-chloroacetylguanidine (120)

To a stirred ice cooled solution of (120) (2.41 g, 10 mmol) in THF (30 ml) was added portionwise sodium hydride (0.25 g, 10 mmol) under nitrogen. The mixture was then warmed to room temperature and the solvent removed to return a red solid. Column chromatography through silica eluting with ethylacetate-methanol returned benzyl alcohol (0.3 g) and 2-amino-1-benzyloxy-4-oxo-2-imidazoline (121) (1.6 g, 80%) mp 165-7°. Nmr δ(DMSO-d6) 3.60 (s, 2H, $-CH_2-$) 4.92 (s, 2H, $PhCH_2$) 7.27 (5H, Ph) 7.85 (1H, N-H exch) and 8.55 (1H, exch) C^{13} ppm (DMSO-d6) 56.5 (t, CH_2) 77.1 (t, Ph-CH_2-) 128.2 (d, arom) 128.4 (d, arom) 129.3 (d, arom) 135.6 (s, arom) 175.5 (s, C = N) and 181.2 (s, C = O). i.r. λ_{max} (KCl) cm^{-1} 3250 (N-H str) 1660-1630 (C = O and C = N str) and 1295 u.v. λ_{max} (EtOH) nm 214 and 235 (10,989). Found: C,58.22; H,5.39; N,20.43; $C_{10}H_{11}N_3O_2$ requires C,58.52; H,5.40; N,20.48%.

Other Attempted Ring Closures of 2-Benzyloxy-1-chloracetylguanidine (120)

With Resublimed Potassium-t-butoxide

To an ice cooled solution of (120) (1.2 g, 5 mmol) in THF (20 ml) was added in one portion resublimed potassium-t-butoxide (0.56 g, 5 mmol) under nitrogen. The mixture was warmed to room temperature and the solvent removed to leave a red solid. Column chromatography through silica afforded 2-amino-1-benzyloxy-4-oxo-2-imidazoline (0.75 g, 75%). By tlc considerable benzyl alcohol was also present in the original reaction mixture.

With Triethylamine

To an ice cooled stirred solution of (120) (1.2 g, 5 mmol) in THF (20 ml) was added dropwise triethylamine (0.7 ml, 5 mmol) in THF (5 ml). By tlc no reaction occurred, heating the solution resulted in the formation of an intractable mixture.

With Sodium Methoxide

A suspension of (120) (300 mg, 1.25 mmol) and sodium methoxide (7.5 mg, 1.40 mmol) in THF (10 ml) was stirred under nitrogen for 24 h. The mixture was then partitioned between ethylacetate and dilute hydrochloric acid. The organic layer was dried (Na_2SO_4) and solvent removed *in vacuo* to return starting material (200 mg).

With Potassium Carbonate

(a) *In Acetone*

A suspension of (120) (300 mg, 1.25 mmol) and potassium carbonate (188 mg, 1.4 mmol) was stirred in acetone (10 ml) for 24 h. Tlc showed largely starting material and a complex mixture of products.

(b) In Methanol

To a solution of (120) (1.68 g, 7 mmol) in methanol (20 ml) was added potassium bicarbonate (700 mg, 7 mmol) and the resulting mixture stirred for 6 h at room temperature under nitrogen. The salt was then filtered off and the filtrate evapourated to dryness in vacuo to leave a yellow solid. Column chromatography of the solid through silica eluting with ethylacetate/methanol 10/1 returned 2-benzyloxyguanidine (2) (from methanol) (750 mg, 67%).

Attempted Ring Closures of 2-Benzyloxy-1-dichloroacetylguanidine (128)

With Sodium hydride

To an ice sooled solution of (128) (500 mg, 1.8 mmol) in THF (10 ml) was added sodium hydride (54 mg, 1.8 mmol, 80% dispersion) under nitrogen. On warming to room temperature tlc showed the gradual formation of a complex mixture.

With resublimed Potassium-t-butoxide

To a stirred ice cooled solution of (128) (275 mg, 1 mmol) in THF (5 ml) was added resublimed potassium-t-butoxide (110 mg, 1 mmol) under nitrogen. Tlc indicated the formation of an intractable mixture.

Debenzylation of (121)

To a solution of (121) (2.05 g, 10 mm) in methanol (50 ml) was added 5% Palladium on charcoal 100 mg (catalytic amount) and the mixture hydrogenated under 1 atmosphere until 10 mmol of hydrogen had been taken up.

The mixture was then filtered through a dicalite pad and the solvent reduced to low volume and 2-amino-1-hydroxy-4-oxo-2-imidazoline (122) filtered off (1.05 g, 91%) mp 164° (violent decomposition). Nmr δ(DMSO-d6) 57.74 (CH), 175.96 (C = N) and 181.66 (C = O). i.r. γ_{max} (KBr) cm^{-1} 3350 (N-H str) 1710 (C = O str, amide) 1650-1630 (C = N str) u.v. λ_{max} (EtOH) nm 212 and 237 (7658). Found: C,31.37; H,4.53; N,36.25; $C_3H_5N_3O_2$ requires C,31.30; H,4.38; N,36.51%.

Attempted Alkylations of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121)

With LDA

To a stirred solution of lithium diisoproylamine (2 mmol) at -78° in THF under nitrogen, was added a solution of (121) (410 mg, 2 mmol) in HMPA (1 ml) and THF (3 ml) and methyl iodide (0.12 ml, 2 mmol). The mixture was stirred at -78° for 30 min. and then gradually allowed to warm to room temperature before leaving to stir overnight. The mixture was then poured into ethyl acetate, washed with dilute acid, then water, dried (Na_2SO_4) and solvent removed to return benzyl alcohol (230 mg). Extensive extractions of the aqueous layer by addition of salt and n-butanol returned HMPA only.

With Dimsyl Sodium

To a solution of (121) (205 mg, 1 mmol) in dry DMSO (5 ml) was added sodium hydride (24 mg, 1 mmol) under nitrogen. The mixture was stirred at room temperature for 10 min., methyl iodide (0.1 ml, 1 mmol) added and then stirred for a further 2 h. The reaction mixture was then poured into ethylacetate and intractable solids filtered off. The filtrate was washed with water, dried (Na_2SO_4) and the solvent removed at reduced pressure to return benzyl alcohol (50 mg).

Removal of all solvents from the aqueous layer under high vacuum with a temperature gradient to avoid high temperatures return an intractable oil (180 mg).

Attempted N-protection of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline with benzyloxy carbonyl

To a solution of (121) (205 mg, 1 mmol) in acetone/water (10 ml/2 ml) was added potassium carbonate (170 mg, 1.1 mmol) and benzyl chloroformate (0.15 ml, 1.1 mmol) under nitrogen. Tlc indicated the gradual decomposition of starting material and formation of benzyl alcohol.

Attempted Protection of 2-Amino-1-hydroxy-4-oxo-2-imidazoline (122) with 2,2-Dimethoxy Propane

A mixture of imidazoline (122), (230 mg, 2 mmol), 2,2-dimethoxy propane (3 ml) and pTSA (30 mg) was refluxed for 1 h. Tlc analysis indicated an intractable mixture.

Preparation of α-Chloropalmitoyl chloride (140)

A mixture of palmitoyl chloride (27.5 g, 0.1 mol), N-Chlorosuccinimide (33 g, mol) and thionyl chloride (30 ml) was refluxed for 2 h under nitrogen. The solution was then cooled to room temperature and succinimide present filtered off. Removal of the solvent left a black oil which on vacuum distillation yielded α-chloropalmitoyl chloride (140) (24 g, 80%) as a pale yellow oil b.p. (165-167°, 0.2 mm Hg). Nmr δ($CDCl_3$) 0.9 (multiplet, 2H, CH_3) 1.10 (multiplet, 26H) (4.41, t, Cl-C-H) i.r. γ_{max} (Ch_2Cl_2) cm^{-1} 1795 (C = O str) M.S. Found 308.1651 $C_{16}H_{30}OCl_2$ requires 308.1674.

Preparation of 2-Benzyloxy-1α-chloropalmitoylguanidine (141)

To a stirred ice cooled solution of benzyloxyguanidine (3.3 g, 20 mmol) and pyridine (1.6 ml, 20 mmol) in dichloromethane (30 ml) under nitrogen was added dropwise over 10 min. a solution of α-chloropalmitoyl chloride

(6.2 g, 20 mmol) in dichloromethane (20 ml). The mixture was stirred for 10 min. at 0°, then warmed to room temperature, poured into water and extracted with dichloromethane, dried (Na_2SO_4) and solvent removed to return an oil. Short path column chromatography through silica eluting with toluene-ethyl acetate returned 2-benzyloxy-1α-chloro-palmitoylguanidine (1.5 g, 34%) (142) mp 35-37°. Nmr δ($CDCl_3$) 0.90 (multiplet, 3H, CH_3) 1.10 (multiplet, 26H) 4.40 (t, 1H, CL-C-H J = 7 Hz) 5.15 (s, 2H, CH_2Ph), 7.30 (5H, Ph) and 8.40 (s, 3H exch). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3490 and 3360 (N-H str), 1710 (C = O str) and 1690 (C = N str) u.v. λ_{max} (EtOH) nm 211 and 253 (1,952) MS Found: 439.2750 $C_{24}H_{40}N_3O_2Cl^{37}$ requires 439.2779 and Found: 437.2770; $C_{24}H_{40}N_3O_2Cl^{35}$ requires 437.2809.

Similarly prepared N-α-Chlorohexanoyl-2-benzyloxyguanidine (143) mp 33-35°

Nmr δ($CDCl_3$) 0.90 (multiplet 2H, CH_3) 1.10 (multiplet, 6H), 4.40 (t, 1H Cl-C-H J = 7Hz) 5.1 (s, 2H, Ch_2Ph) 7.30 (5H, Ph) and 8.40 (5, 3H, exch). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3490 and 3360 (N-H str) 1710 (C = O str) and 1690 (C = N str) u.v. λ_{max} (EtOH) 212 and 253 (2,890) nm. Found: C,56.79; H,6.94; N,13.83; CL,12.08; $C_{14}H_{20}N_3ClO_2$ requires C,56.46; H,6.77; N,14.11; Cl,11.91. MS Found: 297.1235 $C_{14}H_{20}N_3O_2Cl^{35}$ requires 297.1244.

Preparation of 2-Benzyloxy-1α-chloropalmitoylguanidine (141) and 2-benzyloxy-1,3 diα-chloropalmitoylguanide (142)

To a stirred suspension of benzyloxyguanidine (1.61 g, 10 mmol) in peroxide containing ether (100 ml) was added dropwise over 10 min. α-chloropalmitoyl chloride (3.08 g, 10 mmol).

The resultant solution was stirred at room temperature for 30 min. and the solvent removed at reduced pressure to leave an off yellow gum. Column chromatography of the gum through silica eluting with toluene-ethyl acetate returned firstly 1,3-diα-chloropalmitoyl-2-benzyloxy guanidine (142) (0.9 g, 13%) and then 1α-chloropalmitoyl-2-benzyloxy-guanidine (141) (1.0 g, 23%) (from methanol) (141) mp 40-41°. Nmr δ($CDCl_3$) 0.90 (multiplet, 6H, CH_3) 1.1 (multiplet, 52H) 4.40 (t, 2H, Cl-C-H J = 7Hz) 5.20 (s, 2H, CH_2Ph) 7.30 (5H, Ph) and 8.40 (2H, exch). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3370 N-H str 1710 (C = O str) and 1690 (C = N str) u.v. λ_{max} (EtOH) nm 214 and 242 (6977). Found: C,67.28; H,9.78; N,5.70; Calc. C,67.58; H,9.78; N,5.91%. MS Found: 709.4677, $C_{40}H_{69}N_3O_3Cl_2^{35}$ requires 709.4670.

Ring Closure of 2-Benzyloxy-1α-chloropalmitoylguanidine (141)

To an ice cooled solution of (141) (1.1 g, 2.5 mmol) in THF (10 ml) under nitrogen was added in one portion freshly resublimed potassium t-butoxide (600 mg, 3 mmol). The mixture was stirred at 0° for 10 min. and then 30 min. at room temperature. Removal of the solvent left a red gum which on column chromatography through silica eluting with ethylacetate-methanol 10.1 returned 2-amino-1-benzyloxy-4-oxo-5-tetradecyl-2-imidazoline (144), (550 mg, 55%) (from methanol) mp 125-126°. Nmr δ($CDCl_3$) 0.90 (multiplet, 3H, CH_3) 1.15 (multiplet, 26H) 3.80 (t, 1H C-H, J = 6Hz) 4.85 (s, 2H, $PhCH_2$) 5.50-6.50 (broad s, 2H exch) 7.38 (5H, Ph). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3450 (N-H str) 1660-1630 (C = O and C = N str) u.v. λ_{max} (EtOH) nm 214 and 235 (11,200) Calc. C,71.78; H,9.79; N,10.46; Found: 71.28; H,9.84; N,10.61%.

Debenzylation of 2-Amino-1-benzyloxy-4-oxo-5-tetradecyl-2-imidazoline (144)

To a solution of (144) (389 mg, 1 mmol) in methanol (20 ml) was added 5% Palladium on charcoal (40 mg, catalytic amount) and the mixture hydrogenated under 1 atm. for 2 h. The mixture was then filtered through a dicalite pad and the solvent reduced to low volume at reduced pressure and left to crystalise out 2-amino-1-hydroxy-4-oxo-5-tetradecyl-2-imidazoline (145), (290 mg, 94%) mp 142-3°. Nmr δ(DMSO-d6) 0.90 (multiplet, 3H, CH_3) 1.21 (multiplet, 26H) 3.82 (t, 1H, C-H, J = 6Hz) 4.5-5.5 (broad s, 3H, exch). i.r. γ_{max} (KCl) cm^{-1} 3340 and 3150 N-H str 1660 (C = O str) and 1635 (C = N str) u.v. λ_{max} (EtOH) nm 215 and 236 (6834). Found: C,65.32; H,10.55; N,13.06; $C_{17}H_{33}N_3O_2$ requires C,65.55; H,10.68; N,13.49%.

Reaction of 2-Amino-1-benzylox-4-oxo-2-imidazoline (121) with Sodium Hydride

To a solution of (121) (205 mg, 1 mmol) in DMF (5 ml) was added sodium hydride (24 mg, 1 mmol) and the mixture stirred for 30 min. under nitrogen. Removal of the solvent under high vacuum left a gum containing benzyl alcohol as the only tractable product.

Attempted Trapping of Heterocyclic Component Remaining After Elimination of Benzyl Alcohol from 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121) with DMAD

To a stirred solution of (121) (205 mg, 1 mmol) and DMAD (0.13 ml, 1 mmol) in DMF (3 ml) was added in one portion sodium hydride (24 mg, 1 mmol) under nitrogen. Immediately, the reaction turned black. Column chromatography of the mixture through silica eluting with ethyl acetate/methanol returned as indicated by tlc, benzyl alcohol as the only isolable product.

Attempted Acetylation of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121)

To a suspension of (121) (410 mg, 2 mmol) in pyridine (1 ml) was added acetic anhydride (0.2 ml, 2 mmol). Within 5 min. tlc analysis indicated an intractable mixture which was discarded.

Attempted Diazotization of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121)

A mixture of (121) (205 mg, 1 mmol), isoamyl nitrite (0.27 ml, 2 mmol) acetic acid (0.16 ml, 2 mmol) and toluene (10 ml) was refluxed for 24 h under nitrogen. On cooling the mixture, no identifiable products were isolated after column chromatography.

Attempted Diazotization of 3-Amino-1-hydroxy-4-oxo-2-imidazoline (122)

A mixture of (122) (230 mg, 2 mmol), isoamyl nitrite (0.27 ml, 2 mmol) acetic acid (0.16 ml, 2 mmol) and toluene (10 ml) was brought to reflux with stirring under nitrogen. Tlc analysis indicated the gradual formation of intractable products.

Attempted Oxidation of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121) with Mercuric Oxide and Lead Tetra-acetate

A mixture of (121) (205 mg, 1 mmol) and mercuric oxide (270 mg, 1.3 mmol) in THF (10 ml) was left to stir under nitrogen. After 2 days tlc indicated no reaction had occurred. Fresh lead tetra-acetate (260 mg, 1.3 mmol) was then added and the mixture again left to stir under nitrogen. After 8 h tlc indicated an intractable mixture.

Reaction of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121) with Chloroacetyl Chloride

A mixture of (121) (510 mg, 2.5 mmol), Chloroacetyl chloride (0.2 ml, 2.5 mmol) and diethylamino-methyl polystyrene (1.65 g, 5 mmol) was refluxed in THF (10 ml) for 2 h under nitrogen. The solvent was then removed under reduced pressure and the mixture chromatographed through a silica column eluting with ethylacetate to return the bicyclic ring system (148) (220 mg, 36%).

No further purification was attempted and the compound was characterised immediately. mp 65-68° (dec). Nmr $\delta(CDCl_3)$ 3.20 (s, 2H, CH_2), 3.50 (s, 2H, CH_2) 5.20 (s, 2H, CH_2Ph) 7.30 (5H, Ph) C^{13} ppm ($CDCl_3$) 45.75 (t, CH_2) 52.22 (t, CH_2) 78.88 (t, CH_2Ph) 128.45, 128.61, 128.77, 129.37, 129.64,134.57 (aromatic C's) 159.76 (C = N) 167.40 (C = O) and 178.94 (C = O). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 1700 (C = O), 1690 (C = O) and 1670 C = N. M.S. low res M^+ 245.

Attempted Reaction of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline (121) with Methyl Propiolate

Imidazoline (121) (205 mg, 1 mmol) and methyl propiolate (0.085 ml, 1 mmol) were refluxed in THF (10 ml) for 5 days under nitrogen. The solvent was then removed under reduced pressure to leave an intractable red oil (2.90 mg).

Arbuzov Reaction on 2-Benzyloxy-1-chloroacetylguanidine (120)

Guanidine (120) (0.48 g, 2 mmol) was suspended in distilled trimethylphosphite (2 ml) and the mixture stirred at 100° for 3 days under nitrogen. The solvent was then removed *in vacuo* to leave a red gum which was column chromatographed through silica eluting with toluene/ethyl acetate to return 2-(acetyl-1-benzyloxy guanidine) dimethylphosphonate (180) (0.12 g, 18%) as an oil.

Nmr $\delta(CDCl_3)$ 3.00 (d, 2H, $-CH_2-P$, J = 22Hz) 3.85 (d, 6H, $P(OMe_3)_2$ J = 12Hz) 4.90 (s, 2H, CH_2Ph) 6.30 (s, 3H exch) and 7.40 (5H, arom). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3500 and 3360 (N-H_2 str) 1690-1670 (C = O str and C = N str) and 1265 (P = O str) M.S. Found: 315.0979; $C_{12}H_{18}N_3O_5P$ requires 315.0984.

Attempted Preparations of N-Cyanoaziridine (159)

(a) Reaction of Aziridine with Cyanogen Bromide

To a stirred suspension of aziridine (2.15 g, 50 mmol) and calcium carbonate (2.5 g, 25 mmol) in water (180 ml) at room temperature was added portionwise over 30 min. cyanogen bromide (5.3 g, 50 mmol). By i.r. analysis no reaction had occurred.

(b) Reaction of Lithium-Aziridine with Cyanogen Bromide

A solution of methyl lithium (17 ml, 1.3 M, 22 mmol) in ether was added over 1 h to a stirred solution of aziridine (0.95 g, 22mmol) in ether (10 ml) under nitrogen. To the precipitated lithium aziridine was added dropwise a solution of cyanogen bromide (1.95 g, 10 mmol) in ether (10 ml) at 0°. The mixture was warmed to room temperature and left to stir. After 12 h, tlc indicated an intractable mixture.

Formation of 2-bromo-1-cyanamino-1-phenyl ethane (160)

N-Bromosuccinimide (4.28 g, 24 mmol) and cyanamide (6.72 g, 160 mmol) were added to a solution of styrene (2.28 ml, 20 mmol) in dichloromethane (40 ml). The resultant solution was stirred at room temperature for 2 days irradiating with white light.

The mixture was then cooled in an ice bath to ensure complete crystallisation of succinimide which was then filtered off. The solvent was removed from the filtrate in vacuo to yield a yellow oil. Column chromatography on silica gel eluting with petroleum ether-ethylacetate afforded 2-bromo-1-cyanamino-1-phenyl ethane (160) (1.14 g, 43%) as a green oil. Nmr $\delta(CDCl_3)$ 3.60 (d, 2H, J = 6Hz) 4.45 (t, 1H, J = 6Hz) 5.60 (s, 1H, exch) and 7.40 (5H,Ph). i.r. γ_{max} (TF) cm^{-1} 3180 (N-H str) and 2220 (C ≡ N str).

Formation of 2-Phenylaziridine-1-carboxamide oxime (162)

To a stirred ice cooled solution of freshly prepared 1-cyanamino-1-phenyl-2-bromo ethane (15.8 g, 0.07 mol) in THF (800 ml) was added portionwise sodium hydride (1.68 g, 0.07 mol) under nitrogen. The mixture was stirred for 30 min., warmed to room temperature and filtered through a dicalite pad. The filtrate contained 1-cyano-2-phenyl aziridine (161) as a solution in THF which was cooled to 0° in an ice bath and a solution of crystalline hydroxylamine (2.31 g, 0.07 mmol) added dropwise under nitrogen.

The solution was allowed to warm to room temperature and stirred for 2h. Removal of the solvent left 2-phenylaziridine-1-carboxamide oxime (162). (12.3 g, 99%) as a gum. Nmr $\delta(CDCl_3)$ 2.16, 2.70 and 3.22 three spin abx multiplets J_{ax} (trans) 6.70 H_z, J_{bx} (cis) 3.90 H_z and J_{ab} (gem) 0.55 H_z (all $\pm$ 0.05 H_z) 4.58 (3H, exch) and 7.30 (5H, Ph). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3590 (O-H str) 3510 and 3400 (N-H str) 1720 (C = N str) C^{13} ppm ($CDCl_3$) 75.80 (CH_2) 78.34 Ph-C-H 126.70, 127.16, 127.60, 128.09, 128.44 and 138.07 (aromatics) and 158.40 (C = N) M.S. Found 177.0908 $C_9H_{11}N_3O$ requires 177.0902.

Attempted Stabilisation of Aziridine (162)

Hydrochloride Salt

Aziridine (162) (140 mg) was dissolved in dichloromethane (2 ml) and a saturated solution of hydrogen chloride in ether (4 ml) added. Immediately,an intractable gum formed.

Maleic Acid Salt

Aziridine (162) (270 mg, 1.4 mmol) was taken up in the minimum of ethanol and a solution of maleic acid (0.164 g, 1.4 mmol) in the minimum of ethanol added. After 1 h the solvent was removed *in vacuo* to leave an intractable gum.

p-Toluenesulphonic Acid Salt

Aziridine (162) (560 mg, 3 mmol) was dissolved in the minimum of ethanol and a solution of p-toluenesulphonic acid (0.57 g, 3 mmol) in the minimum of ethanol added. The mixture was left to stand for 1 h and the solvent removed to leave an intractable oil.

p-Nitrobenzoyl Chloride

To a suspension of aziridine (162) (354 mg, 2 mmol) and sodium bicarbonate (200 mg, 2mmol) in dichloromethane (20 ml) was added p-nitrobenzoyl chloride (371 mg, 2 mmol). The mixture was left to stir under nitrogen for 2 h whereupon an emulsion formed. The inorganic solid were removed by filtration and the filtrate reduced *in vacuo* to yield an intractable solid (650 mg).

Acetylation

Aziridine (162) (560 mg, 3 mmol) was dissolved in the minimum of pyridine (1 ml), acetic anhydride (0.3 ml, 3 mmol) added and the mixture left overnight.

The solvent was then removed in vacuo to leave an intractable gum.

Methylation

To a solution of aziridine (162) (560 mg, 3 mmol) in dichloromethane (20 ml) was added an etheral solution of diazomethane (7 mmol) and the mixture left overnight. In the morning, a small amount of polymeric material (100 mg) was filtered off. The filtrate was evaporated to dryness in vacuo to return starting material (460 mg).

Ring Expansion of Aziridine (162) to 2-amino-1-hydroxy -5-phenyl-2-imidazoline hydrochloride (163)

A suspension of aziridine (162) (900 mg, 6 mmol) and triethylamine hydrochloride (750 mg, 6 mmol) in acetonitrite (20 ml) was refluxed for 2 h under nitrogen. On cooling to room temperature the crude product was filtered off and dissolved in the minimum of methanol. A saturated solution of hydrogen chloride in ether (10 ml) was then added. The mixture taken to low volume by bubbling through nitrogen and 2-amino-1-hydroxy-5-phenyl-2-imidazoline hydrochloride (163) (600 mg, 47%) filtered off. Mp 190-191°. Nmr δ(DMSO-d6) 3.28 (t, 1H, J = 10Hz), 3.90 (t, 1H, J = 10Hz) 8.44 (t, 1H, J = 8Hz) 7.40 (5H, Ph) and 7.0-8.4 (broad s, 4H, exch) C^{13} ppm (DMSO-d6) 47.8 (t, CH_2) 66.4 (d, C-H) 127.4 (d C-H arom.) 128.5 (d C-H arom.) 136.1 (s, C arom.) and 162.2 (s, C = N). i.r. γ_{max} (KCl) cm^{-1} 3360 and 3290 (N-H str), and 1690 (C = N str) Found; C,50.70; H,5.85; N,19.49% $C_9H_{12}N_3ClO$ requires C,50.59; H,5.66; N,19.67%.

Acetylations of Imidazoline (163) - General Procedure

Imidazoline (163) was suspended in pyridine, acetic anhydride (1, 2 and 3 mol equivalents) added and the mixture stirred for 15 min. at room temperature.

The mixture was then poured into water and extracted with dichloromethane. No further purification could be attained.

2-Acetylamino-1-hydroxy-5-phenyl-2-imidazoline (170)

Nmr δ(DMSO-d6) 1.72 (s, 3H, $CH_3\overset{O}{\overset{\|}{C}}-$) 3.28 (t, 1H, J = 10H), 3.82 (t, 1H J = 10Hz) 4.71 (q, 1H, J = 8Hz) 7.42 (5H, Ph) 5.00-7.00 (broad s, 2H exch). i.r. γ_{max} (KCl) cm^{-1} 1700-1680 (C = O and C = N str) MS Found: 219.0987 $C_{11}H_{13}N_3O_2$ requires 219.1008. Contains fragment 122.0620 C_7H_8NO requires 122.0606.

2-Acetylamino-1-acetyloxy-5-phenyl-2-imidazoline (171)

Nmr δ($CDCl_3$) 2.10 (s, 3H, $CH_3\overset{O}{\overset{\|}{C}}-N$) 2.50 (s, 3H, $CH_3\overset{O}{\overset{\|}{C}}-O$) 3.45 (t, 1H, J = 10$H_2$), 4.25 (t, 1H, J = 10Hz), 4.88 (q, 1H, J = 8Hz) 6.00 (s, 1H, exch) 7.38 (5H, Ph). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 1810 ($CH\overset{O}{\overset{\|}{C}}-O$ str) 1670 ($CH_3\overset{O}{\overset{\|}{C}}-N$ str) low res MS M^+ 261 contains fragment 122.0590 C_7H_8NO requires 122.0606.

3-Acetyl-2-acetylimino-1-acetyloxy-5-phenyl-2-imidazoline (172)

Nmr δ($CDCl_3$) 2.10 and 2.25 (s, $CH_3\overset{O}{\overset{\|}{C}}-N$) 2.50 (s, $CH_3\overset{O}{\overset{\|}{C}}-O$) 3.45 (t, 1H, J = 10Hz) 4.25 (t, 1H, J = 10Hz), 4.88 (q, 1H, J = 8Hz) and 7.38 (5H, Ph). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 1810 ($CH_3\overset{O}{\overset{\|}{C}}-O$ str) and 1670 ($CH_3\overset{O}{\overset{\|}{C}}-N$ str) low res MS M^+ 303, contains fragment 122.0581 C_7H_8NO requires 122.0606.

Attempted Dehydrations of 2-Amino-1-hydroxy-5-phenyl-2-imidazoline hydrochloride (163)

(a) With Diethylaminomethyl polystyrene (solid base)

A suspension of (163) (213 mg, 1 mmol) and diethylaminomethyl polystyrene (340 mg, 1 mmol) in DMF (4 ml) was stirred at room temperature under nitrogen for 24 h. Tlc indicated no reaction had occurred. Thus the mixture was heated to 80° for 1 h whereupon tlc indicated the formation of an intractable mixture.

(b) With Triethylamine and Resin 15 (solid acid)

A suspension of (163) (213 mg, 1 mmol), triethylamine (0.14 ml, 1 mmol) and Resin 15 (200 mg) was stirred in THF (10 ml) at room temperature overnight under nitrogen. Tlc again indicated no reaction had occurred. Thus, the mixture was heated to 80° for 1 h resulting in the formation of an intractable mixture.

(c) With Diethylaminomethyl polystyrene and Resin 15

A suspension of (163) (213 mg, 1 mmol) diethylamino methyl polystyrene (340 mg, 1 mmol) and resin 15 (300 mg) in DMF (5 ml) was stirred at room temperature under nitrogen overnight. The mixture was then filtered to remove solid acid and base. Removal of solvent *in vacuo* returned starting material (213 mg).

Heating the mixture to 60° resulted in an intractable mixture.

Preparation of 2-Amino-1-benzyloxy-4-pyrimidone (181) and (Z)-methyl-3-(2'-benzyloxyguanidino)-2-propenoate (179)

To a stirred ice cooled solution of (2) (1.65 g, 10 mmol) in THF (20 ml) was added dropwise a solution of methyl propiolate (0.85 ml, 10 mmol) in THF (10 ml) under nitrogen.

The mixture was then stirred at 0^{o} for 30 min. before allowing the mixture to warm to room temperature and stir for a further 2 h. Removal of the solvent left a yellow gum which on column chromatography through silica eluting with ethyl acetate/methanol, returned 2-amino-1-benzyloxy-4-pyrimidone (180) (1.3 g, 60%) and 1-benzyloxyguanidino-3-methoxy propenoate (179) (0.5 g, 20%).

1-benzyloxy-2-amino-4-pyrimidone. (from methanol) (181) mp 135-6^{o}. Nmr $\delta(CDCl_3)$; 5.10 (s, 2H, CH_2Ph) 5.55 (d, 1H, = C-H_{cis} J = 6Hz) 6.85 (d, 1H = C-H_{cis}, J = 6Hz), 7.40 (5H, Ph) C^{13} ppm (DMSO-d6); 78.66 (CH_2Ph) 105.91 (d, -C=), 128.34, 129.20, 130.28 and 133.16 (aromatic) 139.17 (d - C=) 152.45 (s, C = N) 168.59 (s, C = O). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3500 (N-H str), 3080 (= C-H str), 1650 (C = O, α,β unsat cyclic) 1640 (C = N), Found: C,60.50; H,5.18; N,19.07; $C_{11}H_{22}N_3O_2$ requires C,60.82; H,5.10; N,19.34%. Found: 217.0846; $C_{11}H_{11}N_3O_2$ requires 217.0851.

(Z)-methyl-3-(2^{1}-benzyloxyguanidino)-2-propenoate (as an oil)(179) Nmr $\delta(CDCl_3)$ 3.65 (s, 3H, OMe) 4.90 (s, 2H, CH_2Ph) 5.45 (d, 1H, = C-H_{trans} J = 15Hz) 7.40 (5H, Ph) 8.20 (d, 1H, = C-H_{trans} J = 15Hz) and 4.50 (s, 3H exch). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3505, 3420 and 3350 (N-H str) 3080 (= C-H str) 2950 (C-H str) 1715 (C = O α,β unsat. acyclic ester) 1665 (C = N str) 1630 (C = C str) 1170 (C-O str). No further purification could be attained.

Preparation of 2-Amino-1-benzyloxy-6-carbomethoxy-4-pyrimidone (187)

To a solution of 2-benzyloxyguanidine (1.65 g, 10 mmol) in THF (10 ml) was added dropwise, a solution of dimethylacetylene dicarboxylate (1.3 ml, 10 mmol) in THF (10 ml) under nitrogen and the mixture stirred for 2 h.

Removal of the solvent left a gum which column chromatographed through silica eluting with ethyl acetate/methanol to afford (187), (from acetone), (2.2 g, 80 %) mp 184° Nmr δ(acetone d6): 3.72 (s, 3H, OMe), 5.25 (s, 2H, CH_2Ph) 5.80 (s, 1H, = C-H) 7.40 (3H, arom) and 7.60 (2H, arom) and 8.20 (2H, exch). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 3460 and 3400 (N-H str), 1740 (C = O str, α,β unsat. ester), 1650 (C = O str, α β unsat. ketone) 1630 (C = N str) and 1170 (C-O str). Found: C,56.87; H,4.81; N, 15.29; $C_{13}H_{13}N_3O_4$ requires C,56.73; H,4.76; N,15.27; M.S. Found 275.0882; $C_{13}H_{13}N_3O_4$ requires 275.0906.

Debenzylation of 2-Amino-1-benzyloxy-4-pyrimidone (181)

To a stirred solution of 4-pyrimidone (181) (440 mg, 2 mmol) in dichloromethane (15 ml) at -78° was added dropwise over a 5 min. period a solution of boron tribromide (0.5 ml, 4 mmol) in dichloromethane (5 ml) under nitrogen. The mixture was stirred for 10 min. at -78° and then warmed to room temperature. Removal of the solvent left an off white solid which was dissolved in methanol (4 ml) and a saturated solution of hydrogen bromide in methanol (5 ml). Reduction of the solvent to low volume left 2-amino-1-hydroxy-4-pyrimidone hydrobromide (182) which was filtered off. (280 mg, 69%) mp 270-2°. Nmr δ(DMSO d6): 6.15 (d = $C-H_{cis}$ J = 9 Hz), 6.60 - 7.80 (broad s, 4H, exch) and 8.15 (d, = $C-H_{cis}$ J = 9Hz) C^{13}ppm (DMSO d6) 102.07 (C=) 145.50 (N-C=) 152.14 (C = N) 163.10 (C = O). i.r. γ_{max} (KCl) cm^{-1} 3600-2000 (broad band) (3240 N-H str) 1701 (C = O str, amide) 1650 (C = N str) u.v. λ_{max} (EtOH) nm 213 and 270 (3828). Found: C,23.02; H,2.91; N,20.19; Br 38.62; $C_4H_6N_3BrO_2$ requires C,23.09; H,2.91; N,20.20; Br 38.42%.

Acetylation of 2-Amino-1-benzyloxy-4-pyrimidone (181)

A solution of 4-pyrimidone (181) (4.3 g, 20 mmol) and acetic anhydride (2 ml, 20 mmol) in pyridine (20 ml) was stirred overnight at room temperature.

The mixture was poured into water, extracted with dichloromethane, dried (Na_2SO_4) and reduced in volume *in vacuo*. Azeotroping with toluene followed by hexane returned 2-acetylamino-1-benzyloxy-4-pyrimidone (193) (4.0 g, 78%) (from dichloromethane-hexane) mp 155-157°. Nmr $\delta(CDCl_3)$ 2.38 (s, 3H, $CH_3\overset{O}{C}$-) 5.20 (s, 2H, CH_2Ph) 5.10 (d, 1H, = C-H_{cis} J = 9Hz) 7.10 (d, 1H, = C-H_{cis} J = 9Hz) 7.48 (5H, Ph) and 8.50 (s, 1H, exch). i.r. γ_{max} (CH_2Cl_2) 1695 (C = O acetyl) 1640-1630 (C = O and C = N str). Calc. C,60.22; H,5.05; N,16.21. Found: C,59.95; H,5.05; N,16.21%.

Attempted Debenzylation of Acetylated 4-pyrimidone (157)

(a) By Hydrogenation

To a solution of the acetylated 4-pyrimidone (0.52 g, 2 mmol) in methanol (20 ml) was added 5% Palladium/Charcoal (50 mg) and the mixture shaken under 1 atm. hydrogen. Within 10 min. an intractable mixture had formed.

(b) By Trimethylsilyl Iodide

A solution of the acetylated 4-pyrimidone (0.26 g, 1 mmol) and triemethylsilyl iodide (1.2 ml, mmol) in carbon tetrachloride (20 ml) was heated at 40° for 30 min. under nitrogen. On cooling, an intractable mixture remained.

(c) By Boron Tribromide

To a solution of the acetylated pyrimidine (0.26 g, 1 mmol) in dichloromethane (20 ml) at -78° was added a solution of boron tribromide (0.25 ml, 2 mmol) in dichloromethane (5 ml) dropwise over a period of 5 min. The mixture was stirred at -78° for 10 min. and then warmed to room temperature and stirred for a further 30 min. Removal of the solvent left crude 1-benzyloxy-2-amino-4-pyrimidone hydrobromide (0.26 g).

Formation of 1-Benzyloxy-2-benzyloxycarbonylamino-4-pyrimidone (197)

To a stirred suspension of (182) (615 mg, 3 mmol) and potassium carbonate (414 mg, 3 mmol) in acetone/water (10 ml/2 ml) was added dropwise a solution of benzyl chloroformate (0.42 ml, 2 mmol) in acetone (4 ml) and the mixture stirred at room temperature for 30 min. The mixture was then poured into dilute ice cold HCl and the precipitated 1-benzyloxy-2-benzyloxycarbonylamino-4-pyrimidone (197) (590 mg, 56%) mp 126-7. Nmr $\delta(CDCl_3)$ 5.15 (s, 4H, CH_2Ph) 5.40 (d, 1H = $C-H_{cis}$ J = 9Hz) 6.90 (d, 1H, = $C-H_{cis}$ J = 9Hz) 7.35 10H, arom 7.10-7.80 (broad s, 1H, exch). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 1700 (C = O str) 1660 (C = O str) and 1610 (C = N str). Calc. C,64.95; H,4.88; N,11.96%. Found: C,65.19 H,5.02; N,11.73, MS Found: 351.1229 $C_{19}H_{17}N_3O_4$ requires 351.1212.

Reaction of (197) with Benzyl Bromide: Formation of 3-benzyl-2-benzyloxy carbonyl amino-4-pyrimidone (198)

A mixture of 4-pyrimidone (197) (175 mg, 0.5 mmol), silver carbonate (140 mg, 0.5 mmol) and benzyl bromide (0.06 ml, 0.5 mmol) was refluxed in toluene in the dark for 5 h under nitrogen. The mixture was then cooled, filtered and the solvent removed in vacuo to leave a gum which on column chromatography through silica eluting with toluene/ethyl acetate 4/1 gave 3-benzyl-2-benzyloxy carbonyl amino-4-pyrimidone (198) (65 mg, 56%) as an oil. Nmr $\delta(CDCl_3)$ 5.12 (s, 2H, $-CH_2Ph$) 5.26 (s, 2H, $-CH_2Ph$) 5.40 (d, 1H, = $C-H_{cis}$ J = 9Hz) 7.02 (d, 1H = $C-H_{cis}$ J = 9Hz) 7.32 and 7.38 (10H, arom). i.r. γ_{max} (CH_2Cl_2) cm^{-1} 1700 (C = O str carboxylic acid) 1650-1630 (C = O and C = N str). M.S. Found: 335.1259 $C_{19}H_{17}N_3O_3$ requires 335.1270.

Attempted Formation of 2-Amino-1-benzyloxy-5-iodo-4-pyrimidone (201)

(a) By Direct Reaction

2-Amino-1-benzyloxy-4-pyrimidones (181) (440 mg, 2mmol) and re-sublimed iodine (500 mg, 2 mmol) was stirred in THF (20 ml) under nitrogen for 2 days.

Tlc and Nmr of an aliquot indicated no reaction. Consequently the mixture was brought to reflux resulting in an intractable mixture.

(b) By Reaction of 2-Benzyloxyguanidine with Methyl Propiolate in the presence of Iodine

To a solution of 2-benzyloxyguanidine (0.82 g, 5 mmol) and re-sublimed iodine (1.27 g, 5 mmol) in THF (20 ml) was added methyl propiolate (0.30 ml, 5 mmol) under nitrogen. By tlc starting material gradually disappeared and an iodine coloured product appeared. On washing with sodium metabisulphite to remove iodine colouration, extraction with dichloromethane returned starting material (0.65 g).

Attempted Diels Alder Reactions of 2-Amino-1-benzyloxy-4-pyrimidone (181)

(a) With Danishefsky's Diene

A solution of 1-methoxy-3-trimethylsilyoxy-1,3-butudiene (0.23 ml, 1 mmol 90%) 4-pyrimidone (181) (0.217 g, 1 mmol) in toluene (10 ml) was refluxed under nitrogen for 2 days. By tlc no reaction had occurred. Consequently titanium chloride (1 drop) was added as a catalyst. A further 24 h reflux returned starting materials. The addition of aluminium chloride as catalyst resulted in de-composition.

(b) With Furan

A solution of 4-pyrimidone (181) (0.217 g, 1 mmol) and furan (0.07 ml, 1 mmol) in toluene (10 ml) was refluxed under nitrogen for 24 h. The reaction mixture was then cooled and starting material filtered off.

Preparation of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline-5-ethanoic acid (207)

A solution of 2-benzyloxyguanidine (2) (1.65 g, 10 mmol) and maleic anhydride (0.98 g, 10 mmol) in THF (20 ml) was stirred overnight under nitrogen. The resultant product was filtered off, hexane added to the mother liquor until precipitation was complete. The combined crops were recrystallised from acetone/hexane to return (207), (2.20 g, 85%) mp 120-2°. Nmr δ(DMSO-d6) 2.62 (d, 2H, CH_2CO_2H) 4.12 (t, 1H, C-H) 4.85 and 4.90 (two s, 2H, CH_2Ph) 7.40 (5H, arom) 3.30 (2H, exch) and 7.80 (1H, exch). i.r. γ_{max} (KCl) cm^{-1} 1700 (C = O str, carboxylic acid) 1680-1660 (C = O str and C = N str) C^{13}ppm (DMSO d6) 63.04 (CH_2) 77.59 (CH_2Ph) 91.91 ($\underset{1}{C}$-N) 126.36, 127.967, 128.20, 128.55, 129.64 and 135.13 (arom) 171.75 (C = N) 174.18 (C = O) and 182.33 (C = O). u.v. λ_{max} (EtOH) nm 216 and 235 (12,282). Found: C,54.51; H,4.88; N,15.86; $C_{12}H_{13}N_3O_4$ requires C,54.75; H,4.98; N,15.96%.

Debenzylation of 2-Amino-1-benzyloxy-4-oxo-2-imidazoline-5-ethanoic acid (207)

To a solution of (207) (200 mg, 0.75 mmol) in methanol (30 ml) was added 5% Palladium/Charcoal (20 mg) and the mixture hydrogenated under 1 atm hydrogen for 1 h. Filtration of the mixture through a dicalite pad and removal of the solvent left 1-hydroxy-2-amino-4-oxo-5-ethanoic imidazoline (209) (125 mg, 97%) mp 145-7°. Nmr δ(DMSO d6) 2.62 (d, 2H, CH_2CO_2H) 3.95 (t, 1H, C-H) 6.00 (s, 5H, exch). i.r. γ_{max} KCl cm^{-1} 3349 and 3295 N-H_2 str 1720 C = O str carboxylic acid 1701 (C = O str). No further purification could be attained.

Preparation of 2-Amino-1,2,4-oxadizaine-5-one dihydrobromide (211)

To a cooled (-78°) solution of (120) (0.72 g, 3 mmol) in dichloromethane (40 ml) was added boron tribromide (0.75 ml, 6 mmol) in dichloromethane (10 ml) dropwise under nitrogen.

The mixture was stirred at -78° for 30 min. before allowing to warm to room temperature. The solvent was then removed to leave (178) (from acetone-hexane) (0.52 g, 63%) mp 265-267°. Nmr δ(DMSO-d6) 4.40 (s, 2H, CH_2) and 6.50-9.00 (broad s, 5H, exch). i.r. γ_{max} (KCl) cm^{-1} 3285 and 3230 (N-H str) 1701 (C = O str) and 1678 (C = N str). u.v. λ_{max} (EtOH) nm 214 (4,453) Found: C,13.01; H,2.49; N,14.68; Br 57.99; $C_3H_7N_3Br_2O_2$ requires C,13.01; H,2.55; N,15.17; Br 57.71%.

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